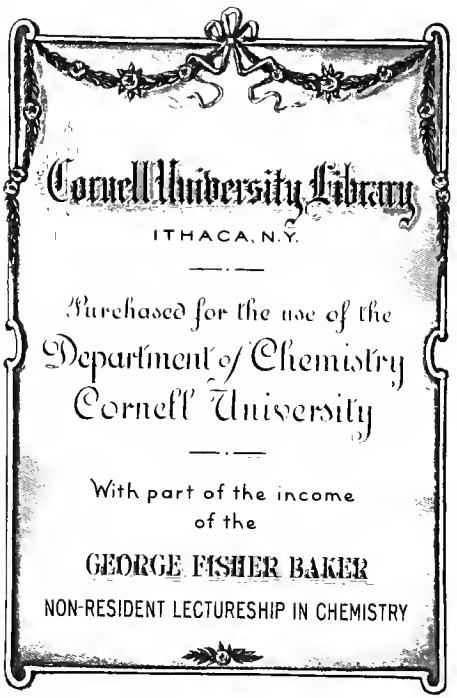

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THE
ORGANIC CHEMISTRY OF NITROGEN

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THE ORGANIC CHEMISTRY OF NITROGEN

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PREFACE

This book originated in lectures given to more advanced students in Oxford. Its object is thus primarily educational, and it is in no sense intended as a work of reference. I have endeavoured to give an account of the present state of knowledge on those parts of the subject which are of the greatest theoretical interest, and at the same time to avoid overloading the text with the names of less important substances. In dealing with the vast group of heterocyclic compounds, I have thought it better not to attempt even an enumeration of all the known types of ring; but I have selected a few of the more important, and discussed these in detail. I have assumed throughout that the reader has at least an elementary knowledge of organic and of general chemistry.

It is becoming generally recognized that organic chemistry cannot be treated satisfactorily without reference to those questions of physical chemistry which it involves. To attempt a separation of the two is to refuse all the assistance which can be derived from what is really the quantitative side of chemistry. The various physical questions are therefore discussed as they arise. A full treatment of the phenomena of tautomerism would have required too great an interruption of the main current of thought; but I have tried to indicate the more important points in which they are illustrated by the bodies under consideration. The dynamics of organic reactions is a field which, in spite of the increasing amount of attention recently devoted to it, is still very largely unexplored; and yet it is of the utmost value for elucidating the mechanism of chemical change. I have therefore made the references to investigations of the velocity of reaction

as complete as I could, and the methods of analysis adopted in each case have been described.

I have to acknowledge my obligations to several of the established textbooks of organic chemistry, and above all to the great *Lehrbuch* of Meyer and Jacobson. I have also made great use of Richter's *Lehrbuch*, and in one or two places I have quoted his admirably concise summaries of the relations of a complicated group of substances. The various monographs dealing with special branches of the subject which I have consulted are referred to in their places.

To my colleagues in Oxford I am indebted for help on various points, more especially dealing with physical questions, and in particular to Mr. D. H. Nagel, for his assistance and advice as the book was passing through the press. I wish to express my heartiest thanks to Mr. H. T. Tizard, who has read the whole work in manuscript, and whose constant suggestions and criticisms have been of the greatest value to me.

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ABBREVIATIONS

Am. Ch. J. American Chemical Journal.
Ann. Liebig's Annalen der Chemie.
Ann. Chim. Phys. Annales de Chimie et Physique.
Arch. d. Pharm. Archiv der Pharmacie.
Atti. R. Atti della Reale Accademia dei Lincei.
Ber. Berichte der deutschen chemischen Gesellschaft.
Brit. Ass. Reports. Reports of the British Association.
Bull. Soc. Bulletin de la Société Chimique de France.
C. Chemisches Centralblatt.
Ch. News. Chemical News.
C. R. Comptes Rendus des Séances de l'Académie des Sciences.
Gazz. Gazzetta Chimica Italiana.
J. Am. Ch. Soc. Journal of the American Chemical Society.
J. C. S. Journal of the Chemical Society.
J. Chim. Phys. Journal de Chimie physique.
J. pr. Ch. Journal für praktische Chemie.
J. Soc. Chem. Ind. Journal of the Society of Chemical Industry.
Mon. Monatshefte für Chemie.
Phil. Mag. Philosophical Magazine.
Pogg. Ann. Poggendorff's Annalen der Physik und Chemie.
Proc. Camb. Phil. Soc. Proceedings of the Cambridge Philosophical Society.
Proc. C. S. Proceedings of the Chemical Society.
Rec. Trav. Recueil des travaux chimiques des Pays-Bas.
Z. f. angew. Chem. Zeitschrift für angewandte Chemie.
Z. f. Elektrochem. Zeitschrift für Elektrochemie.
Zeit. Farb. u. Text. Zeitschrift für Farb- und Textilindustrie.
Z. Ph. Ch. Zeitschrift für Physikalische Chemie.

Alk = Alkyl, C_nH_{2n+1}·
Ar = Aryl, aromatic radical, as $CH_3 \cdot C_6H_4$–.
Ac = Acyl, acid radical, R·CO–.
ϕ = Phenyl, C_6H_5–.
M = Atom of monovalent metal, as K or Na.
Me = Methyl, CH_3–.
Et = Ethyl, C_2H_5–.
CX = Concentration of X (gram-molecules per litre).

THE ORGANIC CHEMISTRY OF NITROGEN

The organic nitrogen derivatives fall naturally into four divisions :—

1. Those in which the carbon is not attached to nitrogen directly, but indirectly, through oxygen. This group is practically confined to the esters of nitrous and nitric acids. (The α-hydroxylamines, $R\text{–}O\text{–}NH_2$, belong strictly speaking to this class, but it is more convenient to discuss them along with the other hydroxylamine derivatives.)

2. Bodies containing one or more nitrogen atoms attached to carbon, but not to one another, and not forming part of a closed ring. These form the most important and fundamental class.

3. Bodies containing two or more nitrogen atoms attached to one another in an open chain.

4. Compounds with closed rings containing one or more nitrogen atoms. Of this enormous class only a selection of the more important types will be discussed.

DIVISION I

COMPOUNDS WITH NO NITROGEN DIRECTLY ATTACHED TO CARBON

CHAPTER I

ESTERS OF NITROUS AND NITRIC ACIDS

ESTERS OF NITROUS ACID

These bodies are formed—

1. By the action of nitrous fumes (a mixture of nitrogen peroxide, trioxide, and nitric oxide) on the alcohols. A modification of this method[1] is to pass the vapour of nitrosyl chloride NOCl into a mixture of the required alcohol and pyridine in molecular proportions. The action of the pyridine is merely to remove hydrochloric acid.

$$O{=}N{\cdot}Cl + HO{\cdot}R = HCl + ONO{\cdot}R.$$

2. By the action of sodium nitrite on a mixture of the alcohol and sulphuric acid.

3. As by-products in the preparation of the nitro-paraffins by the action of silver nitrite on the alkyl iodides.

This curious instance of a tautomeric reaction will be discussed later, in dealing with the nitro-paraffins. At present it may be regarded as a simple double decomposition:—

$$Ag(NO_2) + C_2H_5I = AgI + C_2H_5(NO_2).$$

The nitrous esters are volatile pleasant smelling liquids, which boil at a much lower temperature than the corresponding alcohols. Thus methyl nitrite is a gas, boiling at $-17°$; ethyl nitrite boils at $+17°$, and normal propyl nitrite at $+57°$. On reduction they are split up, with the formation of an alcohol and either hydroxylamine or ammonia. This shows that the nitrogen is not attached to carbon directly, but indirectly, through oxygen, as $CH_3{-}O{-}N{=}O$. If it were attached to the carbon it would remain there on reduction, as it does in the nitro-compounds.

The nitrous esters undergo a singular reaction[2] when treated with excess of zinc or magnesium alkyl halide. An addition-product is formed, which breaks up on treatment with water to give the alcohol of the ester and a β-dialkyl hydroxylamine: the $-N{=}O$ group of the nitrous acid being converted into $-N{=}(Alk)_2$.

$$R{-}O{-}N{=}O + 2\,ZnAlkI \longrightarrow R{-}O{-}N{=}(Alk)_2 \longrightarrow R{-}O{-}H + HO{-}N(Alk)_2.$$

(the intermediate carries OZnI and ZnI)

Among the esters in general those of nitrous acid occupy quite a unique position in respect of the ease with which they are both formed and decom-

[1] Bouveault, Wahl, *C.* **03.** ii. 338.

[2] Bewad, *Ber.* **40.** 3065 (1907).

posed. The formation of an ester from an alcohol and an acid is usually a comparatively slow reaction, which may take several hours or even days. But if a solution of benzyl alcohol (or amyl alcohol) in water is acidified, and then treated with sodium nitrite solution, it instantly becomes milky through separation of the nitrous ester. These esters can also be saponified by strong acids with remarkable rapidity. Indeed the ease with which they break up is shown by the fact that they can be used instead of free nitrous acid, for example in diazotizing; in the same way ethyl nitrite acts on hydrazine in alkaline solution to form hydrazoic acid N_3H.[1]

To explain these and certain other reactions of the nitrous ester Baeyer and Villiger[2] have proposed the following theory. They assume that nitrous acid readily forms unstable addition-compounds in which the nitrogen is pentad. Thus it adds on water to form a compound analogous to phosphorous acid:—

$$O{=}N{-}OH + HOH = O{=}N(OH)_2H.$$

The hydroxyls of this acid can be replaced by alkoxyl or by the anions of acids (including the peroxides), giving rise to such compounds as

$O{=}N(OC_2H_5)(OH)H$ $O{=}N(OSO_2OH)(OH)H$ $O{=}N(OSO_2OH)(OC_2H_5)H$.

These unstable compounds then break up again according to the following rule: if both hydroxyl and alkoxyl are present, the hydroxyl goes out with the hydrogen as water, but if the anion of an acid is present, this remains while the hydroxyl or alkoxyl splits off, as shown by the dotted lines.

This hypothesis explains many remarkable reactions of the nitrites. The rapidity of formation of the esters is due to the occurrence of an addition-reaction, which can take place instantaneously (like most addition-reactions in which trivalent nitrogen becomes pentavalent), followed by the loss of water:—

$$O{=}N{-}OH + HOC_2H_5 = O{=}N(OC_2H_5)(OH)H = O{=}N{-}OC_2H_5 + H_2O.$$

On the other hand the saponification by acids goes thus:—

$$O{=}N{-}OC_2H_5 + HO{\cdot}SO_2OH = O{=}N(OC_2H_5)(OSO_2OH)H$$

$$= C_2H_5OH + O{=}N{-}OSO_2OH \longrightarrow O{=}N\langle{}^{O}_{SO_2OH}.$$

In accordance with the rule H and OC_2H_5 go out to form alcohol, while a tautomeric form of nitrosulphonic acid remains. This is broken up by water into sulphuric and nitrous acids, so that if a substance is present which can react with nitrous acid it will do so; hence the use of nitrous esters in the preparation of diazo-compounds.

[1] Thiele, *Ber.* **41**. 2681 (1908); Stollé, ib. 2811.

[2] *Ber.* **34**. 755 (1901).

The hypothesis also explains an interesting series of reactions of the nitrites with hydrogen peroxide and its organic derivatives. It is found that while (1) ethyl nitrite and hydrogen peroxide give alcohol and nitric acid, (2) ethyl hydroperoxide, $C_2H_5O{\cdot}OH$, and nitrous acid give ethyl nitrate and water. Now if the hydrogen peroxide broke up, in adding on to the nitrous acid, into two hydroxyls, one would get in both reactions the same addition-product:—

(1) $O{=}N{-}OC_2H_5 + (OH)_2 \rightarrow$

(2) $O{=}N{-}OH + \begin{matrix} OC_2H_5 \\ | \\ OH \end{matrix} \rightarrow$ $O{=}N(OH)(OC_2H_5)$

and hence the same ultimate product. The fact that the products are different shows that the peroxide breaks up (like the sulphuric acid in the previous case) into $H + O{\cdot}OH$, which gives:—

$$(1)\ O{=}N{-}OC_2H_5 + H{\cdot}OOH = O{=}N(OC_2H_5)(O{\cdot}OH)(H) = O{=}N{-}OOH + C_2H_5OH.$$

This again breaks up, in accordance with the rule that OOH like the anion of an acid remains attached to the nitrogen, into alcohol and a peracid $O{=}N{-}O{\cdot}OH$, which then changes into nitric acid: the ultimate products from the nitrite and hydrogen peroxide being nitric acid and alcohol, as experiment shows they are. On the other hand nitrous acid and ethyl hydroperoxide react thus:—

$$(2)\ O{=}N{-}OH + H{\cdot}OOC_2H_5 = O{=}N(OOC_2H_5)(OH)(H) = O{=}N{-}OOC_2H_5 + H_2O$$

giving the ester of the peracid, which changes into ethyl nitrate: and this again is in accordance with experiment. This view is strikingly confirmed by the action of ethyl hydroperoxide on amyl nitrite. If the peroxide acted only as an oxidizing agent it would of course produce amyl nitrate; whereas if it split up into $H + O{\cdot}OC_2H_5$ it should give ethyl nitrate thus:—

$$O{=}N{-}OC_5H_{11} + H{\cdot}OOC_2H_5 = O{=}N(OC_5H_{11})(H)(O{\cdot}OC_2H_5)$$

$$\rightarrow O{=}N{-}O{\cdot}OC_2H_5 \rightarrow O{=}N{<}\begin{matrix} O \\ OC_2H_5 \end{matrix}.$$

As a fact only ethyl nitrate was obtained.

This theory is not definitely established, but it certainly appears to offer a plausible explanation of the very peculiar behaviour of nitrous acid and its esters.

The rate of formation and of hydrolysis of the alkyl nitrites has been measured by W. M. Fischer,[1] the amount of ester being determined by titration. He finds that these reactions though very rapid are not instantaneous. Ethyl nitrite is hydrolysed by water, but not completely so; thus an N/43 solution of the ester is 84 per cent. hydrolysed. In presence of hydrochloric acid the hydrolysis is practically complete, but the first titration was found to be about 6 per cent. higher than that obtained after five minutes, which was also the final value. This indicates a very high velocity, which

[1] *Z. Ph. Ch.* **65**. 61 (1908).

may be compared with that of the hydrolysis of triphenyl-methyl chloride to the carbinol. The reactions seem to be of the same order as in other cases, since the usual expression

$$\frac{C_{alcohol} \times C_{acid}}{C_{water} \times C_{ester}} = \text{const.}$$

was found to hold good.

On the other hand soda and sodium ethylate act on the ester comparatively slowly. The velocity constant obtained with aqueous soda is only about three times as great as that for ethyl acetate; while with sodium ethylate in absolute alcohol the velocity is only about one-fortieth of this, and is actually only a tenth of that observed with the ethyl ester of ethyl sulphonic acid.

The esters of nitrous acid undergo a remarkable condensation, in presence of sodium or potassium ethylate, with compounds containing an acidic methylene group, such as phenyl-acetic ester, giving the salt of an oxime[1]:—

$$C_2H_5{\cdot}O{\cdot}NO + \phi{\cdot}CH_2{\cdot}CO_2C_2H_5 + KOC_2H_5 = 2\ C_2H_5OH + \phi\text{–}C\langle\begin{matrix}NOK\\CO_2C_2H_5\end{matrix}.$$

Baeyer and Villiger[2] have also drawn attention to a singular analogy between nitrous acid and triphenyl-carbinol $(C_6H_5)_3COH$. They both form esters with alcohols with unusual ease. They both combine with sulphurous acid to give sulphonic acids, $NO{\cdot}SO_3H$, $\phi_3C{\cdot}SO_3H$. The carbinol with aniline forms an anilide $\phi_3C{\cdot}NH\phi$, as nitrous acid with secondary amines forms a nitrosamine $ON{\cdot}NR_2$. With phenols it condenses to oxy-tetraphenyl-methane $\phi_3C{\cdot}C_6H_4OH$, as nitrous acid does to a nitrosophenol, $ON{\cdot}C_6H_4OH$. Triphenyl-methyl chloride, like nitrosyl chloride, gives double salts with metallic chlorides. Finally, corresponding to the free monovalent radicle NO there is (probably) the free monovalent radicle ϕ_3C, Gomberg's triphenyl-methyl.

ESTERS OF NITRIC ACID

The esters of nitric acid, like those of other mineral acids, can be prepared by the direct action of the acid on the alcohol; but in this case special precautions are required. The nitric acid generally contains nitrous acid, and in any case this is likely to be formed by the reduction of some of the nitric acid by the alcohol; and in the presence of nitrous acid the ester is violently oxidized, which diminishes the yield and may easily lead to violent explosions. To avoid this danger the acid may be previously purified by distillation in vacuo with concentrated sulphuric acid, and then the alcohol dropped into it, the temperature not being allowed to rise above 5°;[3] or, as in the preparation of the aromatic nitro-compounds, the alcohol may be dropped into a mixture of nitric and sulphuric acids kept at 0°.

A more usual method is to add some substance which will destroy the nitrous acid as fast as it is formed. The substance employed is urea, which

[1] W. Wislicenus, Grützner, *Ber.* **42**. 1930 (1909).
[2] *Ber.* **35**. 3019 (1902).
[3] Bouveault, Wahl, *C.* **03**. ii. 338.

has the advantage of giving with nitrous acid only nitrogen, carbon dioxide, and water:

$$O{=}C(NH_2)_2 + 2\ O{=}NOH = CO_2 + 2\ N_2 + 3\ H_2O.$$

The nitric acid is first boiled with urea, and then more urea is added and the alcohol dropped in.

The nitric esters of the lower alcohols are colourless, pleasant smelling liquids, whose boiling-points are a good deal higher than those of the corresponding nitrites, and not far removed from those of the alcohols themselves:—

	Alcohol	Nitrate	Nitrite
methyl	+ 65°	+ 66°	− 12°
ethyl	78°	87°	+ 17°
n-propyl	97°	110·5°	57°
i-propyl	81°	101·5°	39°
n-butyl	117°	136°	75°

When set on fire they burn with a white flame, and when heated above their boiling-points they explode violently. On reduction with tin and hydrochloric acid they give the alcohol and hydroxylamine, showing that the nitrogen is attached to the carbon through oxygen: $CH_3{-}O{-}N\langle^{O}_{O}$: this is also proved by the ease with which they are saponified by acids to alcohol and nitric acid, though these primary products react with one another to some extent, forming oxidation products of alcohol, such as aldehyde, and nitrous acid. The same thing happens on alkaline saponification[1]; and in this case it is probable that a certain amount of ethyl hydroperoxide $C_2H_5O{\cdot}OH$ is formed. They condense (like the nitrites) in presence of sodium or potassium ethylate, with bodies containing an acidic methylene group, to form isonitro-compounds[2]:—

$$EtO{-}NO_2 + NaOEt + \phi{\cdot}CH_2{\cdot}CO_2Et = 2\ EtOH + \phi{-}C\langle^{NO{\cdot}OK}_{CO_2Et}.$$

Among the nitric esters some are of great practical importance—certain polynitrates of the polyatomic alcohols. The simplest of these is glyceryl trinitrate

$$\begin{array}{l} CH_2{-}O{-}NO_2 \\ | \\ CH{-}O{-}NO_2 \\ | \\ CH_2{-}O{-}NO_2 \end{array}$$

commonly, though wrongly, called nitroglycerine. It is formed by the action of a mixture of nitric and sulphuric acids on glycerine. It is an oily liquid, without colour or smell, which solidifies at + 8°. It is scarcely soluble in water. On saponification[3] the NO_3 groups are readily split off as nitric acid, but they oxidize the glycerine, and are themselves reduced to nitrous acid. If the ester is set on fire it burns away rapidly but quietly: but under certain definite conditions it can be made to explode with great violence.

[1] Gutmann, *Ber.* **41**. 2052 (1908); Tor Carlson, *C.* **09**. i. 933; Cambi, *C.* **09**. ii. 693.
[2] W. Wislicenus, Endres, *Ber.* **35**. 1755 (1902); Wislicenus, Grützner, *Ber.* **42**. 1930 (1909).
[3] See Robertson, *Ch. News*, **99**. 289 (1909).

Another class of nitric esters used for explosives consists of the nitrocelluloses. Cellulose is a carbohydrate which forms the chief constituent of the walls of plant cells. Its molecular weight is unknown, but is very high, and it is quite possible that under this name are included several allied but distinct substances. Common forms of it are cotton-wool and Swedish filter-paper. Cellulose contains hydroxyl groups, and therefore when treated with strong nitric acid or a mixture of nitric and sulphuric acids it is converted into a series of nitric esters, whose constitution is proved by the fact that they give nitric acid when treated with alkalies, and that under the action of reducing agents they split off their nitrogen and re-generate cellulose.[1] The nitration may occur in several stages,[2] and in order to designate the products the molecular formula of cellulose is assumed to be $C_{12}H_{20}O_{10}$ (it is of course really a high polymer of this); and to this their formulae are referred. Thus we have cellulose dinitrate, $C_{12}H_{18}O_8(NO_3)_2$, tetranitrate, $C_{12}H_{16}O_6(NO_3)_4$, and hexanitrate, $C_{12}H_{14}O_4(NO_3)_6$. Higher nitration-products than the hexanitrate cannot be obtained. These various stages can be separated by means of their solubility in certain solvents, such as alcohol, ether, and ethyl acetate; but it is probable that the products so obtained are themselves mixtures and not chemical individuals. They all possess the property, which is characteristic of the organic polynitrates in general, of being highly explosive.

The less nitrated compounds, the di- and tetranitrates, which are got by treating cotton-wool with a mixture of nitric and sulphuric acids of a definite strength, are soluble in a mixture of alcohol and ether: and this solution is known as collodion. If the solvent is allowed to evaporate the nitrocellulose remains behind as a firm and continuous film. It is on this property that its use in surgery and in the older wet-plate process of photography depends. A solution of this feebly nitrated cellulose in molten camphor constitutes the celluloid which is used nowadays for so many purposes. It has the advantage that it can be worked into almost any form, but its use is somewhat dangerous, since, as we should expect from its composition, it catches fire very readily and burns with great violence.

The more highly nitrated celluloses, the tetra- to the hexanitrate, form the well-known explosive gun-cotton. With comparatively few and unimportant exceptions all modern explosives are made out of nitrocellulose and nitroglycerine. The history of the development of this branch of applied chemistry has been described by Will,[3] from whose paper the following facts are taken.

In 1846 Schönbein discovered that cotton, when treated with a mixture of nitric and sulphuric acids, was converted without any change in its external appearance into a powerful explosive, which had many advantages over gunpowder. It was more stable, it burnt without smoke, and it had a much

[1] Some so-called nitrocelluloses are, however, possibly nitrates of oxy-cellulose, an oxidation-product of cellulose. Vignon, *C.* **03**. i. 1081.

[2] Cf. Hake, Bele, *Journ. Soc. Chem. Ind.* **28**. 457 (1909).

[3] *Ber.* **37**. 268.

greater explosive power. The first difficulty met with in its preparation was the complete removal of the nitrating acids: for if these are not removed, the gun-cotton rapidly decomposes, not unfrequently with violent explosions. This was got over by Abel's method (1865) of grinding up the nitrocellulose with water and then compressing it.

The next difficulty was firing the gun-cotton. The ordinary method of firing by a train of gunpowder through the touch-hole frequently failed to do more than make it burn away rapidly. Nobel overcame this in 1864 by using a small initial charge of black powder, fired by a silver fulminate detonator. He soon found that the detonator alone was sufficient, without the initial charge. The same method could also be used to fire nitroglycerine, which had been discovered about the same time as gun-cotton (Sobrero 1848), but for nearly twenty years afterwards had not been employed as an explosive, owing to the peculiar difficulties which it offered, from the fact of its being a liquid. In 1865, however, Nobel showed that 'Kieselgur', a fine porous infusorial earth, would absorb three times its weight of nitroglycerine to form a substance of the constituency of putty, which was easily packed into cartridges, and was much less sensitive to blows than nitroglycerine itself. This he called dynamite. It at once came into use on an enormous scale for blasting purposes, as is shown by the following figures, which give the total production of dynamite in the world:

1867	11 tons
1874	3,000 tons
1899	62,150 tons.

The Kieselgur which is used in dynamite to give a solid consistency to the nitroglycerine is of course a perfectly inert substance and diminishes correspondingly the energy of the explosive. Hence Nobel endeavoured to replace it by some solid explosive. In 1878 he found that if collodion, a solution of the less nitrated cellulose in ether and alcohol, is mixed with nitroglycerine and the solvent allowed to evaporate, an indiarubber-like mass of great explosive energy is formed. This constituted his 'gelatinized dynamite', which soon replaced ordinary dynamite to a very large extent. Shortly afterwards he found that nitroglycerine would 'gelatinize' with nitrocellulose without the employment of any solvent at all. The cellulose does not dissolve, but it absorbs the nitroglycerine and swells up in the same sort of way that gelatine does when treated with cold water. Ballistite and cordite are explosives prepared in this way.

The use of these explosives for guns was at first impossible from their very high rate of combustion. In order to secure the maximum velocity for a given strength of barrel it is necessary that the pressure of the gases should not be put on too suddenly, but should continue to rise as long as it can act on the projectile; in other words the charge must go on burning as long as the shot is in the gun. With the increase in the size of ordnance difficulties arose in this way even with the old black powder, and the rate of combustion of nitrocellulose is far higher. It was therefore necessary to find some means for making the rate of combustion slower, and, moreover, for regulating it to

the particular value required for each gun. Now it has been shown that an explosion started in a piece of explosive gelatine proceeds in concentric spheres from the point of origin, and hence it is obvious that if the substance is cut up into thin strips the rate of decomposition will be diminished. In this way the difficulties were finally overcome, and it was found possible to use the nitro-powders for cannon, as well as for mining purposes. It is to be noticed that the gelatinized powders are peculiarly suitable for modification in this way: not only because their consistency makes it easy to give them any required form, but also, which is even more important, because this form is retained during the explosion; whereas powders of a more or less crystalline character, like black powder, are broken up by the pressure of the gases into fine particles, and thus the effect of the form which is originally given to them is largely destroyed.

Acyl Nitrates

A recently discovered class[1] of nitric acid derivatives are the nitrates of the acid radicles, such as acetyl nitrate, $CH_3{\cdot}CO{\cdot}ONO_2$, and benzoyl nitrate, $C_6H_5{\cdot}CO{\cdot}ONO_2$. They are made by the action of nitrogen pentoxide on the acid anhydride, or of silver nitrate on the acid chloride, in the cold. Acetyl nitrate is a fuming colourless liquid, boiling at 22° under a pressure of 77 mm. Benzoyl nitrate is a yellow oil.

They resemble the acid chlorides in being violently decomposed by water into the organic acid and nitric acid. They explode on sudden heating, and are very powerful nitrating agents.

Another mixed anhydride of acetic and nitric acids is the so-called diacetyl-ortho-nitric acid,[2] $(CH_3{\cdot}CO{\cdot}O)_2{\cdot}N(OH)_3$, which is formed by the action of acetic anhydride on nitric acid. It is a liquid boiling at 128°, and is also a powerful nitrating agent.

[1] Francis, *J. C. S.* **1906**. 1; *Ber.* **39**. 3798; Butler, *Ber.* **39**. 3804 (1906); Pictet, Khotinsky, *C. R.* **144**. 210; *Ber.* **40**. 1163 (1907).

[2] Pictet, *C.* **02**. ii. 1438; **03**. ii. 419, 1108; Pictet, Genequand, *Ber.* **35**. 2526.

DIVISION II

BODIES CONTAINING ONE NITROGEN ATOM ATTACHED TO CARBON

CHAPTER II

AMINES

All these bodies may be regarded as derived from ammonia or hydroxylamine by the replacement of hydrogen by organic radicals: or from nitrous or nitric acid by the replacement of the hydroxyl. The various classes will be dealt with in order, beginning with the most highly reduced, that is, the derivatives of ammonia, the amines and amides.

By replacing one, two, or three of the hydrogen atoms in ammonia by hydrocarbon radicals we obtain the three classes of primary, secondary, and tertiary amines. Moreover the nitrogen may become pentad, and so we may have a fourth hydrocarbon group attached, giving rise to the quaternary ammonium compounds.

The first amine to be discovered was aniline, prepared by Unverdorben[1] in 1826, by the distillation of indigo; its constitution was made out by Hofmann[2] in 1843. Of the fatty amines, the primary were discovered by Wurtz[3] in 1848, who prepared them by the hydrolysis of the isocyanates: and the three other classes by Hofmann,[4] by the action of the alkyl halides on ammonia.

Methods of Formation

1. Hofmann's method, by heating the alkyl halides with alcoholic ammonia:—

$$\begin{aligned} C_2H_5I + NH_3 &= C_2H_5NH_2\cdot HI \\ C_2H_5I + C_2H_5NH_2 &= (C_2H_5)_2NH\cdot HI \\ C_2H_5I + (C_2H_5)_2NH &= (C_2H_5)_3N\cdot HI \\ C_2H_5I + (C_2H_5)_3N &= (C_2H_5)_4NI \end{aligned}$$

This method cannot be used with aromatic halides on account of the firmness with which the halogen is attached: unless negative groups (such as nitro-groups or other halogen atoms) are present, whereby this firmness is diminished.

Both primary and secondary alkyl iodides can be used in this reaction; but tertiary cannot, as they give no amine, but lose hydriodic acid and form alkylenes.

This reaction gives rise to a mixture of all the four classes of derivatives, for which special methods of separation are required, which will be discussed later. The proportions in which the various possible products are formed

[1] *Pogg. Ann.* **8.** 397. [2] *Ann.* **47.** 37. [3] *Ann.* **71.** 330.
[4] *Ann.* **73.** 91 (1850); **74.** 159 (1850); **78.** 253; **79.** 16 (1851).

constitutes a very complicated physico-chemical problem,[1] since they are determined partly by the relative velocities of reaction of the intermediate products, and partly by the solubilities of the substances in the solvent employed. In some cases a suitable selection of conditions enables one to obtain mainly the particular base required; but often (as in this case of the ethyl amines) a mixture of all possible substances is got, which must afterwards be separated by chemical means.

A modification of this method is to heat the alcohols to 250–260° with the compound of zinc chloride and ammonia[2]:—

$$R{\cdot}OH + NH_3 = R{\cdot}NH_2 + H_2O.$$

The aromatic amines can thus be obtained from the phenols at about 330°. This reaction is used for preparing amines of the naphthalene series.

It is also possible to prepare methylamine by the direct alkylation of ammonia in aqueous solution with methyl sulphate in presence of alkali.[3]

2. There are a series of reactions which depend on starting with an imido-compound whose imide hydrogen atom can be replaced by a metal. If this metal is replaced by an alkyl group and the body so formed is saponified, an amine is obtained. There are three important reactions of this kind.

a. By boiling the isocyanic esters with potash. Isocyanic acid is the imide of carbonic acid, as urea is its amide:—



Carbonic acid Urea Isocyanic acid

Silver (iso)cyanate acts on ethyl iodide to give ethyl isocyanate, and this hydrolyses to ethylamine and carbon dioxide:—

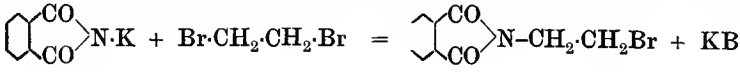
$$C_2H_5{\cdot}N{=}C{=}O + H_2O = C_2H_5{\cdot}NH_2 + CO_2.$$

It was by this reaction that Wurtz discovered the fatty amines in 1848.

b. Similarly the isocyanides when treated with alkali give the amine and formic acid:—

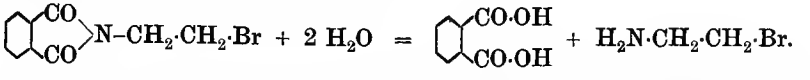
$$C_2H_5{\cdot}N{=}C + H_2O = C_2H_5{\cdot}NH_2 + H{\cdot}CO{\cdot}OH.$$

c. A method much used in recent years for obtaining amines which are otherwise difficult to prepare, is Gabriel's phthalimide reaction. Phthalimide is prepared from phthalic anhydride and ammonia gas. If it is dissolved in absolute alcohol and treated with alcoholic potash, potassium phthalimide is precipitated. If this is treated with, say, ethylene dibromide in molecular proportions, the metal is replaced by the group $CH_2{\cdot}CH_2Br$:—



[1] Pinner, Franz, *Ber.* **38.** 1539 (1907). [2] Merz, Gasiorowski, *Ber.* **17.** 623 (1886).
[3] Burmann, *Bull. Soc.* [3] **35.** 801 (1906).

When the product is treated with fuming hydrochloric acid it splits up into phthalic acid and brom-ethylamine:—



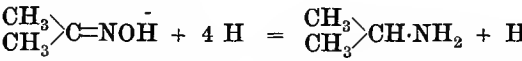
3. Reduction of bodies containing nitrogen doubly or triply linked to carbon. (This naturally cannot be used to prepare aromatic amines.)

a. Reduction of nitriles: most conveniently with sodium and alcohol. (Mendius reaction.)

$$C_2H_5{\cdot}C{\equiv}N + 4\,H = C_2H_5{\cdot}CH_2{\cdot}NH_2.$$

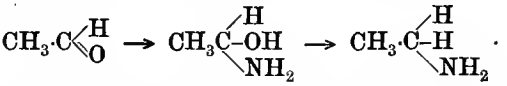
It may also be carried out[1] by passing the vapour of the nitrile mixed with hydrogen over powdered nickel at 180–220°, whereby a mixture of primary, secondary, and tertiary amines and ammonia is formed, the secondary amine predominating.

b. Reduction of the oximes:—



This can also be done[2] by means of hydrogen gas in presence of heated nickel or copper.

A reaction which may be compared with this, though it does not properly belong to this group, is the reduction of the aldehyde-ammonias, which are really *α*-oxy-amines:—



This is used to some extent commercially,[3] the aldehyde being mixed with aqueous ammonia and the solution electrolysed.

c. Reduction of hydrazones: for example that of acetone:—

$$(CH_3)_2C{=}N{-}NH\phi + 4\,H = (CH_3)_2CH{\cdot}NH_2 + H_2N\phi.$$

It is a general rule that whenever a body containing a chain of two nitrogen atoms is reduced, they separate from one another.

4. Reduction of nitro-compounds. This is of the greatest importance in the aromatic series, but it can also be used for the fatty compounds:—

$$R{\cdot}NO_2 \longrightarrow R{\cdot}NH_2.$$

5. Finally, there are two very peculiar reactions leading from the amide or azide of an acid to an amine with one atom of carbon less. Their mechanism will be discussed in detail later.

a. The Hofmann reaction,[4] starting with the amide. This is dissolved in bromine, and then distilled with excess of potash. There are various intermediate stages,[5] but the result is that the CO group of the amide is oxidized by the bromine to CO_2 and eliminated:—

$$R{\cdot}CO{\cdot}NH_2 + Br_2 + H_2O = R{\cdot}NH_2 + CO_2 + 2\,HBr.$$

The primary amine goes over mixed with some ammonia, but free from

[1] Sabatier, Senderens, *C. R.* **140.** 482 (1905). [2] Mailhe, *C. R.* **140.** 1691; **141.** 113 (1905).
[3] Knudsen, *C.* **03.** ii. 271; **04.** i. 134. [4] *Ber.* **15.** 762 (1882). [5] See p. 82.

secondary and tertiary amines. It is collected in hydrochloric acid, and purified by extraction with absolute alcohol, in which ammonium chloride is practically insoluble. The yield in the lower series is excellent, but in the higher is bad, as the bromine then removes hydrogen from the amine to form the nitrile (reversal of the Mendius reaction).

$$R{\cdot}CH_2{\cdot}NH_2 + 4\,Br = R{\cdot}C{\equiv}N + 4\,HBr.$$

b. The Curtius reaction [1] is similar to this. If the acid azide is boiled with hydrochloric acid, it breaks up into nitrogen, carbonic acid, and the amine:—

$$R{\cdot}CO{\cdot}N_3 + H_2O = R{\cdot}NH_2 + CO_2 + N_2.$$

It has been shown by Forster [2] that this reaction is probably due to the intermediate formation of an isocyanate, which can actually be isolated in some cases:— $R{\cdot}CO{\cdot}N_3 \longrightarrow N_2 + R{\cdot}N{=}C{=}O \longrightarrow R{\cdot}NH_2 + CO_2$.

Properties

The boiling-points of some of the simpler amines are given in the following table [3]:—

	Mono-	Di-	Tri-amine.
methyl	− 7°	+ 7°	+ 3·5°
ethyl	+ 19°	+ 56°	+ 90°
propyl	49°	110°	156°
isopropyl	32°	84°	—
isoamyl	95°	187°	235°
n-octyl	176°	297°	366°

The lower members are very soluble in water, and have a smell resembling that of ammonia, though often very unpleasant. They are not easy to distinguish from ammonia except by the fact that they burn: it was in this way that Wurtz discovered that the gas he obtained from ethyl isocyanate was not ammonia, as he had for some time supposed. As the molecular weight increases, the smell and the solubility in water diminish. The alkylamines are distinct bases,[4] with an alkaline reaction to litmus, and they absorb carbon dioxide from the air. These properties are not shared by the aromatic amines, which are much less basic. In fact the successive introduction of alkyl groups into ammonia increases the basicity, while that of aromatic groups diminishes it.

The alkylamines precipitate the hydroxides of many metals from solutions of their salts, but not always the same metals as ammonia. They form stable salts with mineral acids. It is remarkable that Hantzsch [5] has found by the boiling-point method that the molecular weight of dimethyl-ammonium chloride, $(CH_3)_2NH_2Cl$, dissolved in chloroform is in a 1 per cent. solution

[1] *Ber.* **27.** 778 (1894); **29.** 1166 (1896).
[2] *J. C. S.* **1909.** 433.
[3] Meyer, Jacobson, *Lehrb.* **I.** 1. 354.
[4] At low temperatures (−75°) they seem to be capable of forming acid salts with two or three molecules of haloid acid. See Korczyński, *Ber.* **41.** 4379 (1908); Kaufler, Kunz, *Ber.* **42.** 385 (1909).
[5] *Ber.* **38.** 1045 (1905).

three times, and in a 3 per cent. solution four times that required by the simple formula.

Many amines also combine with water to form stable hydrates (of the type RNH_3OH, corresponding to NH_4OH) which can be dried with potassium carbonate without breaking up. These hydrates are generally oily liquids, which only lose water when treated with potash or barium oxide.

Methods of separation of the various classes of amines

The quaternary compounds are easily removed by distilling the mixed salts with potash. The primary, secondary, and tertiary amines pass over, while the quaternary hydroxides, not being volatile, remain behind.

A general method for the separation of primary, secondary, and tertiary amines is that of Hinsberg,[1] which depends on their behaviour with benzenesulphonic chloride, $C_6H_5SO_2Cl$. The mixed bases are treated with an equivalent quantity of this reagent, and shaken with potash till the smell of the chloride disappears. The acid chloride reacts with the amines as it does with ammonia, the chlorine being eliminated along with the hydrogen attached to the nitrogen (the potash assists the reaction just as it does in the Schotten-Baumann method of benzoylation). As there is no such hydrogen in the tertiary amines the sulphonic chloride does not react with them at all. With the primary and secondary amines it replaces one H by ϕSO_2, giving with the primary $RNH{\cdot}SO_2\phi$, and with the secondary $R_2N{\cdot}SO_2\phi$. This last is insoluble in potash, while the derivative of the primary amine, which still has a hydrogen atom attached to the nitrogen, is soluble, since the strongly negative phenyl-sulphonyl group makes this hydrogen acidic. Thus on extracting the alkaline solution with ether, the tertiary amine is removed along with the phenyl-sulphonyl derivative of the secondary, from which it can be separated by distillation; while the derivative of the primary remains in solution, and can be precipitated by acid. The amines can be recovered from these derivatives by heating with strong acid.[2]

There is no other general method[3] of separation, but there are a variety of special methods for use in particular cases, of which the best known is that employed by Hofmann for separating the ethylamines. It is remarkable that although the boiling-points of the three ethylamines lie so far apart (19°, 56°, and 90°) Hofmann found that it was impossible to separate them by fractional distillation even when he used more than a kilogram of the mixed amines. This must be due to their vapour pressures falling very gradually with the temperature.

To separate them, the dry mixture of bases is heated with dry ethyl oxalate. Triethylamine does not react, and can be distilled off. The other two react in different ways, diethylamine giving diethyl-oxamethane, $\begin{matrix}CO{\cdot}NEt_2\\ |\\ CO{\cdot}OEt\end{matrix}$

[1] *Ber.* **23.** 2962 (1890). [2] Cf. Hinsberg, Kessler, *Ber.* **38.** 906 (1905).

[3] For a method of identifying the various classes of amines by the action of Grignard's reagent, see Sudborough, Hibbert, *J. C. S.* **1909.** 477. For another method, see v. Braun, *Ber.* **41.** 2156 (1908).

and ethylamine diethyl-oxamide, $\begin{matrix}CO\cdot NHEt\\ |\\ CO\cdot NHEt\end{matrix}$. The reason for this difference is unknown. (The best way of remembering it is to observe that both the products have two ethyl groups attached to nitrogen.) On extracting the mass with water, the diethyl oxamide dissolves, while the ester does not; and if the aqueous solution is boiled with potash it gives oxalic acid and ethylamine, while from the residue the diethylamine can be obtained by a similar process of saponification.

Chemical properties of the alkylamines

The reactions of the four classes are in general very different, since they largely depend on the hydrogen remaining attached to the nitrogen; thus in many cases tertiary amines do not react at all.

This hydrogen on the nitrogen can be replaced by sodium or potassium, giving rather unstable compounds. It can also be replaced by acyl groups, forming substituted amides, on treatment with acid anhydrides or chlorides:—

$$C_2H_5NH_2 + (CH_3\cdot CO)_2O = C_2H_5\cdot NH\cdot CO\cdot CH_3 + CH_3\cdot COOH.$$

This is also true of the aromatic amines.

Primary and secondary fatty amines react with carbon bisulphide to give alkyl-sulphocarbamic acids:—

$$\begin{matrix}C_2H_5\cdot NH_2\\ C_2H_5\cdot NH_2\end{matrix} + \begin{matrix}C{=}S\\ \|\\ S\end{matrix} = \begin{matrix}C_2H_5\cdot NH\\ C_2H_5NH_3S\end{matrix}\!\!>\!C{=}S$$

the acid forming a salt with a second molecule of the amine. Aromatic amines behave in a different way. These salts, if they are formed from a primary amine, as in the above example, break up when treated with mercuric chloride thus:—

$$\begin{matrix}C_2H_5\cdot NH\\ C_2H_5NH_3S\end{matrix}\!\!>\!C{=}S = \begin{matrix}C_2H_5N{=}C{=}S\\ +\\ C_2H_5NH_2\end{matrix} + H_2S$$

giving an amine and an isothiocyanate or mustard oil, which can be detected by its peculiar smell. This is Hofmann's 'mustard oil' reaction for detecting primary amines.

Another test of Hofmann's for primary amines, which goes equally well with alkyl and aryl amines, is the isonitrile reaction. The amine is heated with chloroform and alcoholic potash, when the isonitrile is formed, which is recognized by its smell:—

$$C_2H_5NH_2 + CHCl_3 = C_2H_5N{=}C + 3\,HCl.$$

A fraction of a drop of amine is sufficient for this test.

The behaviour of the three classes of amines with nitrous acid is very characteristic. As usual, the nitrous acid, $HO\cdot N{=}O$, can react with either end of its molecule, the hydroxyl going out as water with one hydrogen atom or the oxygen atom with two.

The primary alkylamines form water, nitrogen, and the alcohol:—

$$C_2H_5NH_2 + O{=}NOH = C_2H_5OH + N_2 + H_2O.$$

A nitrite is of course formed as an intermediate product, and it has recently

been shown by Wallach [1] that these nitrites are much more stable than is generally supposed, and if prepared in absolutely neutral solution can often be isolated, especially in the case of the polymethylene derivatives; though they are rapidly decomposed by small quantities of acid. The alcohol produced is often an isomer of what one would expect: for example, a secondary instead of a primary. This peculiar change has been investigated by Henry.[2] He finds that normal propylamine gives 58 per cent. of isopropyl alcohol and only 42 per cent. of the normal alcohol; $(CH_3)_2CH{\cdot}CH_2{\cdot}NH_2$ gives 75 per cent. of trimethyl carbinol $(CH_3)_3C{\cdot}OH$, and 25 per cent. of isobutyl alcohol; while $(CH_3)_3C{\cdot}OH$ is wholly converted into $C_2H_5(CH_3)_2C{\cdot}OH$. In other words, the larger the number of methyl groups attached to the carbon atom next but one to the amino group the greater the extent to which this change takes place.

In the polymethylene derivatives the ring is often affected. Thus trimethylene-amine gives allyl alcohol [3]:—

$$\begin{matrix}CH_2\\|\\CH_2\end{matrix}\!\!>\!CH{\cdot}NH_2 \longrightarrow CH_2{=}CH{\cdot}CH_2{\cdot}OH.$$

More commonly the ring increases in size, a 3-ring becoming a 4-ring [4]:—

$$\begin{matrix}CH_2\\|\\CH_2\end{matrix}\!\!>\!CH{\cdot}CH_2{\cdot}NH_2 \longrightarrow \begin{matrix}CH_2{\cdot}CH_2\\|\quad\quad|\\CH_2{\cdot}CH{\cdot}OH\end{matrix}$$

or a 5-ring a 6-ring [5]:—

$$\begin{matrix}CH_2{\cdot}CH_2\\|\quad\quad\\CH_2{\cdot}CH_2\end{matrix}\!\!>\!CH{\cdot}CH_2{\cdot}NH_2 \longrightarrow \begin{matrix}CH_2{\cdot}CH_2{\cdot}CH_2\\|\quad\quad\quad|\\CH_2{\cdot}CH_2{\cdot}CH{\cdot}OH\end{matrix}$$

On the other hand a 6-ring will apparently not go into a 7-ring; for Wallach finds [6] that when cyclohexylamine $C_6H_{11}{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$ is treated with nitrous acid the ring is not altered, the product consisting of a mixture of the alcohols $C_6H_{11}{\cdot}CH_2{\cdot}CH_2{\cdot}OH$ and $C_6H_{11}{\cdot}CHOH{\cdot}CH_3$, together with a small quantity of the olefine $C_6H_{11}{\cdot}CH{=}CH_2$.

Secondary amines with nitrous acid give nitrosamines:—

$$(C_2H_5)_2N{\cdot}H + HO{\cdot}NO = H_2O + (C_2H_5)_2N{\cdot}NO.$$

Here also a nitrite is no doubt an intermediate product; and in one case, that of di-isopropylamine, the salt $[(CH_3)_2CH{-}]_2NH_2{\cdot}O{\cdot}NO$ has been isolated.

The tertiary amines, having no hydrogen on the nitrogen, do not react with nitrous acid at all.

The amine hydrogen of the primary and secondary amines can be replaced by chlorine on treatment with bleaching powder, giving such compounds as $CH_3{\cdot}NCl_2$, which must have its chlorine attached to nitrogen since with zinc methyl it gives trimethylamine. These bodies are explosive, but much less so than nitrogen chloride, and they can often be distilled unchanged. The chlorine is very loosely attached to the nitrogen, as is shown by the

[1] *C.* **07.** ii. 54. [2] *C. R.* **145.** 899, 1247 (1907). [3] Kishner, *C.* **05.** i. 1703.
[4] Demjanow, *Ber.* **40.** 4393 (1907). [5] Wallach, *C.* **07.** ii. 54.
[6] *Ann.* **359.** 287 (1908).

fact that on warming with concentrated hydrochloric acid it is replaced by hydrogen, the amine being reproduced:—

$$C_5H_{11}NHCl + HCl = Cl_2 + C_5H_{11}NH_2.$$

The hydrochloric acid here behaves as a reducing agent, like hydriodic acid. Other compounds with chlorine attached to trivalent nitrogen are reduced by hydrochloric acid in the same way.

When the haloid salts of the amines are heated to a high temperature, alkyl halide is split off. If there are several alkyls present including methyl, it is always the methyl which comes off. This fact is made use of in preparing methyl chloride on the large scale from the trimethylamine of the beet sugar residues.

Of the individual alkylamines methylamine, the simplest, can be made by passing a mixture of hydrocyanic acid and hydrogen over platinum black at 110°.

The one with the longest chain is heptadecylamine, $C_{17}H_{35}NH_2$. It melts at 49° and boils at 335°. It is as basic as the lower amines. Its alcoholic solution absorbs carbon dioxide from the air, and has a strong alkaline reaction. But its hydrochloride, though easily soluble in alcohol, is insoluble in water, whereas the hydrochlorides of the lower amines are deliquescent.

QUATERNARY AMMONIUM COMPOUNDS

They were discovered by Hofmann as the final product of the action of the alkyl halides on alcoholic ammonia. They may be made by acting with the alkyl halides on the tertiary amines. The reaction goes with very different ease in different cases: thus trimethylamine combines with methyl chloride at the ordinary temperature with evolution of heat, but it will not combine with ethyl chloride at the ordinary temperature at all. The velocity of reaction of triethylamine with ethyl iodide to form tetra-ethyl-ammonium iodide was investigated in great detail by Menschutkin.[1] He found that it was enormously affected by the solvent. Thus it was 720 times as great in acetophenone as in hexane.

The other salts are generally got from the iodide by treatment with the silver salt of the acid in question. They mostly crystallize well. The haloid salts all break up on heating into tertiary amine and alkyl halide. If one of the alkyls is methyl, it is always methyl halide that is split off, as happens with the salts of the other amines also.

The quaternary hydroxides are strong bases. It is often said that they are so strong that they cannot be prepared from their salts by the action of potash. This is not true; only as both products, the quaternary hydroxide and the potassium salt, are soluble, it is not easy to isolate them in this way. It is however possible in some cases to get the hydroxide to crystallize out. The usual method of preparation is to treat the iodide with moist silver oxide:—

$$NMe_4I + AgOH = NMe_4OH + AgI.$$

The silver iodide is filtered off and the solution evaporated.

[1] *Z. Ph. Ch.* **6**. 41. (1890).

They resemble potash to an extraordinary degree. They form deliquescent crystalline masses; their aqueous solution turns red litmus blue, and absorbs carbon dioxide readily. It dissolves the skin and saponifies fats.

When heated the hydroxides are converted into tertiary amines, one alkyl being split off. If this is a methyl, it appears as methyl alcohol; but in all other cases the alcohol which may be supposed to be formed breaks up further into water and alkylene, for example:—

$$(CH_3)_3N\langle^{CH_2\cdot CH_3}_{OH} = (CH_3)_3N + CH_2{:}CH_2 + H_2O.$$

It is to be noticed that if one of the alkyls is a methyl, it remains attached to the nitrogen; whereas, as we have seen, when the hydroxyl is replaced by halogen, the methyl group is the first to come off.

As there is a certain amount of evidence for the existence of free 'ammonium', NH_4, in ammonium amalgam, attempts have been made to isolate tetramethyl-ammonium, $N(CH_3)_4$, which we should expect to be more stable. These have not succeeded, but it has been shown[1] that if a solution of tetramethyl-ammonium chloride (free from alkali) in liquid ammonia is electrolysed, deep blue layers are formed at the cathode, similar to those produced by dissolving sodium in liquid ammonia. In the latter case the blue compound, which is formed without evolution of hydrogen, is probably the substituted ammonium, NH_3Na. Hence it is probable that in the former case the blue substance is the analogous tetramethyl-ammonium, $N(CH_3)_4$. Similarly, it is found[2] that metallic caesium dissolves in liquid methylamine at very low temperatures to form a blue liquid, no doubt containing CH_3NH_2Cs; but when the temperature rises to $-20°$ the colour disappears and hydrogen is evolved, the substituted metalamide $NHCH_3Cs$ being left behind.

A question which may be conveniently discussed in connexion with the quaternary ammonium compounds is that of the structure of ammonium compounds and of pentavalent nitrogen derivatives in general. The earlier supporters of the theory of constant valency held that nitrogen was triad, and explained the existence of the quaternary derivatives by calling them molecular compounds. This view was generally abandoned when in 1876 V. Meyer and Lecco[3] showed that the same body was obtained from trimethylamine and ethyl iodide as from ethyl-dimethylamine and methyl iodide. It was then recognized that nitrogen in these compounds had a valency of five. Recently however some chemists, especially Werner,[4] have introduced a view not unlike that of molecular compounds. Werner supposes that in ammonium chloride, for example, the whole hydrochloric acid molecule is attached to the ammonia by a new kind of bond; and he writes it $NH_3 \ldots HCl$, or more recently $\left[\begin{smallmatrix}H\\H\end{smallmatrix}\rangle N\langle^{H}_{H}\right]Cl$; the group enclosed in the bracket is the cation: the dotted line in this last formula is intended to show that one of the four groups is attached to the nitrogen in a different way. All these

[1] Palmaer, *Z. f. Elektrochem.* **8.** 729 (1902). [2] Rengade, *C. R.* **140.** 246 (1905).

[3] *Ann.* **180.** 173.

[4] Cf. *Ann.* **322.** 276 (1902); *Lehrb. d. Stereochemie*, p. 310 (1904). Hantzsch also inclines to the same view; *Ber.* **38.** 2161 (1905).

suggestions of new species of valencies are to be regarded with grave suspicion. They are usually advanced to account for some class of reactions which is not yet thoroughly understood, and we should be cautious of accepting them until there is a great mass of evidence in their support, and until we are quite certain that we cannot explain the facts without them. It is safe to say that at present of all the various new types of linkage which Werner, Baeyer, and others have offered to us, not one has yet made good its claims. (This does not, of course, apply to Thiele's theory of conjugate links, which is only an extension of the ordinary structural theory.)

At the same time it is worth considering the evidence which has been adduced in support of this view of the structure of the pentavalent nitrogen compounds. Hantzsch[1] has argued in its favour from the behaviour of the dibromides of the tertiary amines. Trimethylamine combines with bromine to form a dibromide $(CH_3)_3NBr_2$. When this is treated with potash, we should expect it to give first the compound $(CH_3)_3N\langle^{OH}_{Br}$, a well-known body, obtained from the amine-oxide $(CH_3)_3N{=}O$, and convertible into it by the further action of alkali. But the dibromide with potash does not give this body, nor the amine-oxide. It breaks up into trimethylamine, potassium bromide, and potassium hypobromite. Hantzsch regards this as a proof that it cannot have the formula $(CH_3)_3N\langle^{Br}_{Br}$, and he writes it on Werner's model $\left[\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!N\!\!<\!\!\begin{matrix}CH_3\\Br\end{matrix}\right]Br$, whereby the action of potash on it—

$$[(CH_3)_3N{\cdot}Br]Br \longrightarrow [(CH_3)_3N{\cdot}Br]OH \longrightarrow (CH_3)_3N + HOBr$$

appears analogous to the action of potash on trimethylamine hydrobromide:—

$$[(CH_3)_3N{\cdot}H]Br \longrightarrow [(CH_3)_3N{\cdot}H]OH \longrightarrow (CH_3)_3N + HOH.$$

This is ingenious, but we can surely explain the reaction without having recourse to this new hypothesis. These dibromides readily break up again into their components, the tertiary amine and bromine, as Hantzsch admits, and therefore the body might react with potash in two different ways:—

$$(CH_3)_3NBr_2 \begin{cases} \nearrow (CH_3)_3N\langle^{OH}_{Br} \\ \searrow (CH_3)_3N + Br_2 \longrightarrow (CH_3)_3N + KBr + KOBr. \end{cases}$$

Which of these two reactions actually occurs will depend on their relative velocities, as to which nothing is known. As we find that the second takes place, this must be the quickest. The assumption of a new type of valency seems quite unnecessary.

Another argument of more value is derived from the influence of the successive introduction of alkyls on the basicity of the amine hydrates. This quantity requires some explanation. The statements to be found in the textbooks as to the strength of organic bases are often misleading. They are frequently based on qualitative evidence, such as the readiness of formation of salts with weak acids, where many other factors are concerned besides

[1] *Ber.* **38.** 2154 (1905).

the actual strength of the base; and even where they depend on a measurement of the concentration of the hydroxyl ions, as in Bredig's work, they are affected by a disturbing influence which for a long time escaped notice. A primary, secondary, or tertiary amine, R_3N, when dissolved in water undergoes two changes. It takes up water to form the quaternary hydroxide, and this then dissociates electrolytically:—

$$\underset{x}{R_3N} + H_2O \leftrightharpoons \underset{y}{R_3N\begin{matrix}H\\OH\end{matrix}} \rightleftarrows \underset{z}{R_3NH'} + OH'.$$

Now if x be the concentration of the amine R_3N, y of the ammonium hydrate R_3NHOH, and z of the ions, we know that

$$\frac{x}{y} = \text{constant}, = b.$$

Further, from Ostwald's law $\frac{z}{y} = K$.

The real strength of the base is given by K. But in the ordinary methods for determining basicity we measure z, the concentration of the ions, in a solution in which the total concentration of the base in all three forms is known, the existence of the first form, the non-hydrated tertiary base R_3N, being neglected. The value of the strength calculated from this is not the true K, but what may be called the apparent strength, K_1, $= \frac{z^2}{x + y}$.

But since $x = by$, $K_1 = \frac{z^2}{by + y}$,

$$= \frac{z^2}{y(b + 1)},$$

$$= K \times \frac{1}{b + 1}.$$

Hence the apparent strength of the base is smaller than the real strength, and the more so the greater the proportion of anhydrous amine present. When therefore the strength of an organic base (other than quaternary) is spoken of, what is meant is the product of two factors, the hydration constant and the dissociation constant. And until recently there was no method known for determining either of these two factors separately. The measurement of the ionization is no use, as the hydration factor comes in to the same extent at every dilution. The determination of the partition-coefficient between water and air or an organic solvent has been suggested; but this does not help us either. The concentration of the R_3N in the other solvent is proportional to that of the R_3N in the water, and therefore also to that of the R_3NHOH: which leaves us where we were before. The problem has at length been solved by Moore.[1] He points out that all methods of solution must fail, in which the observations are all made at the same temperature. If however we measure the partition-coefficients and the degree of dissociation at different temperatures, and if we further make the assumption, which for small differences of temperature is justifiable, that the temperature-

[1] *J. C. S.* **1907**, 1373.

coefficients of these two quantities are constant, we obtain a sufficient number of equations to solve the problem. In this way we can determine for any amine (and the method applies equally to all pseudo-acids and pseudo-bases, and to such bodies as carbonic acid and the lactones) the proportion present in the non-hydrated form, and the true dissociation-constant. So far, the necessary data have only been obtained for three substances, piperidine (which does not concern us at present), ammonia, and triethylamine. The results show that in an aqueous solution of ammonia at 20°, about two-thirds is present as non-hydrated NH_3, the rest being mainly NH_4OH and a small quantity of ions; in the case of triethylamine only about a third is in the anhydrous form, as $(C_2H_5)_3N$. From these data the true dissociation constants of these two bases can be calculated, and are found to be at 20°:—

Ammonia $K = 5{\cdot}23 \times 10^{-5}$
Triethylamine 64×10^{-5}.

That is to say, the introduction of three ethyl groups into ammonia has increased the constant only twelve-fold. We should therefore expect that the introduction of a fourth ethyl group, in tetra-ethyl-ammonium hydroxide, would involve a further increase only to about 150×10^{-5}, which would mean that it was still a very weak base. But as a fact the quaternary hydroxide is an excessively strong base, comparable to potash, for which K is too high to be measured and is certainly greater than 1. It therefore appears that the first three ethyl groups produce only a small increase in the basicity of ammonium hydrate, while that produced by the fourth is enormous. It has long been known that the quaternary bases were far stronger than the others, but until the true dissociation-constants had been determined it was possible that this might be due to the unknown quantity of anhydrous base present in the latter cases but not in the former. This is no longer possible; and the sudden increase in the quaternary bases certainly seems to point to a difference between their constitution and that of the hydroxides of the primary, secondary, and tertiary amines. If we are not prepared to accept a formula such as Werner's, there are two possible explanations. One is that the data on which these calculations are based (especially those for triethylamine) may be incorrect. But even if they are to be accepted, and this sudden change of basicity really occurs, it can be explained on the assumption of analogous structures for the tertiary and quaternary hydroxides, and without having recourse to any new theories of valency. If we say that the five valencies of pentavalent nitrogen are all equal, this only means that the relation between any five groups and the nitrogen atom is determined by those groups themselves, so that (excluding stereoisomerism) isomeric arrangements are impossible. It is nevertheless quite conceivable, and indeed probable, that three of the nitrogen valencies (those of trivalent nitrogen) are essentially different from the other two: and that when successive alkyl groups are introduced into ammonium hydrate they fill up these three places first. If so, the introduction of a fourth group, which must now take up one of the other two positions, may be expected to produce an effect on the molecule different from that produced by any of the other three.

Another phenomenon which is no doubt connected with the formation of hydrates is the remarkable effect of temperature on the solubility of certain amines in water.[1] When a liquid is not completely miscible with water, it is almost invariably found that with a rise of temperature the solubilities both of the liquid in water and of water in the liquid increase, until a point is reached at which they become completely miscible. But there are certain amines (triethylamine, diethylamine, β-collidine) for which these relations are reversed. At low temperatures they are completely miscible with water, but on warming, separation into two layers takes place, and with a further rise of temperature the solubility of each substance in the other diminishes; although there are indications that at a still higher temperature their mutual solubilities begin to increase again. In the case of nicotine[2] both phenomena are combined. Below 60° and above 210° nicotine is miscible with water in all proportions: but between these two temperatures it is only partially soluble. The fact that these peculiar phenomena occur to a marked extent only with substances of the same chemical type suggests that they depend on a chemical reaction; and it is fairly obvious that this is the formation of a hydrate. On the analogy of the quaternary hydroxides we should expect triethyl-ammonium hydroxide, Et_3NHOH, to be excessively soluble in water, while the anhydrous triethylamine, containing no hydroxyl, should be comparatively insoluble. A rise of temperature will no doubt increase both these solubilities, as this is its effect in all normal cases: but at the same time it will increase the proportion of anhydrous to hydrated base. Indeed Moore has shown for triethylamine that the proportion of base present as Et_3N is at 15° 30 per cent., and at 35° over 50 per cent. Thus the total effect of raising the temperature is greatly to increase the proportion of the much less soluble form; and this may well overcome the other effect (on the solubility of that form) and cause the total solubility to diminish. On the other hand, at a much higher temperature, where the dissociation into anhydrous base and water is practically complete, and it is really the solubility of the anhydrous base alone that is being measured, the second effect may be expected to predominate, and the solubility to begin to increase again, as happens in the case of nicotine. This explanation is much strengthened by the fact that the only liquids other than amines which show, though to a much smaller extent, a marked diminution of solubility with rise of temperature, are certain ketones and lactones, which from their structure should be capable, though in a much lower degree, of forming hydrates by the oxygen becoming tetravalent.

STEREOCHEMISTRY OF PENTAVALENT NITROGEN

The quaternary ammonium compounds[3] are of special interest from their bearing on the stereochemistry of nitrogen. As early as 1877 Wislicenus pointed out that van 't Hoff's theory of asymmetric carbon should be capable

[1] Rothmund, *Z. Ph. Ch.* **26.** 433 (1898). Lattey, *Phil. Mag.* [6] **10.** 397 (1905); *J. C. S.* **1907.** 1959. Flaschner, *Z. Ph. Ch.* **62.** 493 (1908).

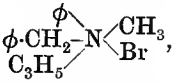
[2] Hudson, *Z. Ph. Ch.* **47.** 113 (1904).

[3] Cf. Wedekind, *Zur Stereochemie des fünfwertigen Stickstoffes* (Leipzig, 1907).

of extension to the case of pentavalent nitrogen. But for twenty years all efforts to discover cases of stereoisomerism among the pentavalent nitrogen compounds were unsuccessful. (The case of the trivalent nitrogen derivatives will be discussed under the oximes.) In 1891 Le Bel[1] claimed to have obtained an optically active form of isobutyl-propyl-ethyl-methyl-ammonium chloride by the action of moulds; but no one else has been able to repeat his work. In 1899 Wedekind[2] obtained two inactive but apparently stereoisomeric forms of benzyl-allyl-methyl-phenyl-ammonium bromide, differing in melting-points and physical properties generally. As no other analogous compounds could be obtained in isomeric forms, and as further neither of these two isomers could be converted into the other, doubt was thrown on the work, and it was repeated by Hantzsch and Horn,[3] who confirmed Wedekind's conclusions. Recently, however, both Wedekind[4] himself and H. C. Jones[5] have shown that the second of these supposed isomers is really benzyl-phenyl-dimethyl-ammonium bromide, the allyl group being expelled by the methyl in the course of the preparation.

There have been several other supposed cases of this kind, of inactive isomerism of completely asymmetric ammonium compounds, depending on the order in which the various groups are introduced; but they have all been shown to be erroneous, although such bodies often give two dimorphic crystalline forms.[6]

The first optically active nitrogen compounds were obtained by Pope and Peachey[7] in 1899. Wedekind had previously tried to resolve his benzyl-phenyl-allyl-methyl-ammonium salt (the true one) by fractional crystallization of its salts with active acids, but in vain. Pope and Peachey employed the same method in non-aqueous solvents, in order to avoid the effect of dissociation, and they used dextro-camphor-sulphonic acid and its bromo-derivative, which have the advantage of being both powerfully active and also very strong acids. The iodide of Wedekind's base, dissolved in a mixture of acetone and ethyl acetate, was treated with the silver salt of this acid, and thus converted into its d-camphor sulphonate. This salt was then fractionally crystallized from the same solvent, and so separated into the less soluble salt of the dextro-base and the more soluble salt of the laevo-base. These bodies on treatment with potassium iodide or bromide are converted into the iodide or bromide, which are found to be optically active in solution. In these latter salts, for instance in the bromide

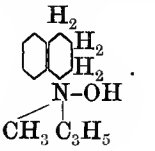


there is no possible asymmetric carbon atom; and thus it is conclusively proved that the phenomenon of optical activity in solution is not confined to carbon, but is shared by nitrogen as well.

[1] *C. R.* **112.** 724. [2] *Ber.* **32.** 517. [3] *Ber.* **35.** 883 (1902).
[4] *Ber.* **39.** 481 (1906). [5] *J. C. S.* **1905.** 1721.
[6] Cf. Le Bel, *J. Chim. Phys.* **2.** 340 (1904); Kipping, *J. C. S.* **985.** 628; Schryver and Collie, *Ch. News*, **63.** 174.
[7] *Proc. C. S.* **15.** 192; *J. C. S.* **1899.** 1127.

It is to be noticed that the activity is retained in the platinum and silver double salts.

Since 1899 there have been many attempts to prepare the active forms of ammonium compounds of this type. Some of them have failed, but a good many have been successful, so that by now we have more than a dozen quaternary ammonium compounds known in their two active forms. It is evident that all bodies of the type $R_1R_2R_3R_4NX$ are capable of giving two active modifications, but in many cases one changes into the other too easily for separation to be possible. It should also be possible to get activity when two of the four hydrocarbon groups are replaced by the two parts of a carbon ring of which the nitrogen forms part; this has recently been realized by Buckney[1] and Wedekind,[2] who have separated the two forms of the salts of allyl-kairolinium (allyl-methyl-tetrahydro-quinolinium) hydroxide:—



In solution the asymmetric bodies lose their activity more or less rapidly, a phenomenon originally attributed to the change of one antimer into the other, and known as auto-racemization. This has been investigated by Wedekind,[3] who found it to be due to a monomolecular reaction. It proceeds much faster in chloroform than in alcohol. It is affected by the nature of the acid radical; the free base (hydroxide), the chloride, bromide, and iodide all change, the iodide the quickest; while the nitrate, the camphor-sulphonate, and apparently the fluoride, do so much more slowly or not at all. It is also of course affected by the nature of the base. In the series which Wedekind investigated, the alkyl-phenyl-methyl-benzyl-ammonium compounds, the racemization is much more rapid when the alkyl is isobutyl than when it is allyl or normal propyl.

Later work[4] has shown that the primary cause of this change is the dissociation of the quaternary salt into tertiary amine and alkyl halide:—

$$R_4N{\cdot}Br \longrightarrow R_3N + R{\cdot}Br.$$

This dissociation can be followed by means of the fall in the amount of halogen ion, by titrating the solution from time to time with silver. It is found that the diminution of activity is proportional to the fall in the amount of silver solution required, showing that the undissociated salt is wholly in the original active form. Measurements of the molecular weight by the cryoscopic method, and of the conductivity, confirm these results. The temperature coefficient of the velocity constant in these cases is unusually high, being between 4 and 5 for 10°. The solvents used were in most cases

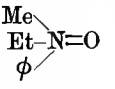
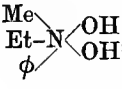
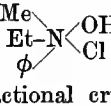
[1] *Proc. Camb. Phil. Soc.* **14**. 177; *C.* **07**. ii. 820. [2] *Ber.* **40**. 4450 (1907).

[3] *Stereochemie*, p. 72; *Z. f. Elektrochem.* **12**. 330 (1906).

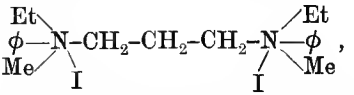
[4] v. Halban, *Z. f. Elektrochem.* **13**. 57 (1907); *Ber.* **41**. 2417; E. Wedekind, Paschke, ib. 2659 (1908).

chloroform and bromoform; in solvents of greater ionizing power, such as alcohol and water, the dissociation does not seem to take place.

At the same time it may be pointed out that though these results show that the primary reaction is a dissociation, a true racemic change must ultimately ensue. The dissociation is reversible, as an amount of salt varying in different cases from 6 to 40 per cent. was found to remain undissociated at equilibrium. Hence the tertiary amine and the alkyl halide must recombine: and as they are themselves inactive, they must produce a racemic mixture of the dextro and laevo salt. It is thus to be expected that the activity will ultimately disappear entirely, while the silver titre will not.

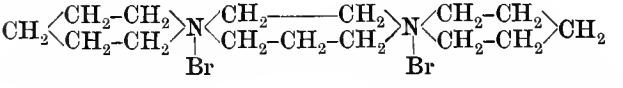
A very remarkable extension of the conditions of activity of pentavalent nitrogen has recently been made by Meisenheimer.[1] He prepared methyl-ethyl aniline oxide, a basic substance of the formula  or  , which forms salts with acids of the type  . The d-brom-camphor-sulphonate of this base was divided by fractional crystallization into two parts, from which two active chlorides (of the above formula) were prepared. This was so far a new discovery, that it was the first case of an active nitrogen compound in which two of the five different groups attached to the nitrogen were negative. A far more unexpected result is that if this salt is treated in solution with baryta, whereby it is practically entirely converted into the weak base $R_3N{=}O$ or $R_3N\langle^{OH}_{OH}$, the activity remains. On either formula there are only four different groups attached to the nitrogen, and yet the compound is active.

The stereochemical analogy between carbon and nitrogen has been carried beyond the simple case of a single asymmetric nitrogen atom. E. and O. Wedekind have shown that the compound obtained from methyl iodide and trimethylene-di-ethylaniline



which contains two asymmetric nitrogens with symmetry in the molecule, occurs in two inactive modifications, differing in physical properties. These must correspond to racemic and mesotartaric acids: one of them should be capable of being broken up into two active antimers, but attempts to carry this out have failed.

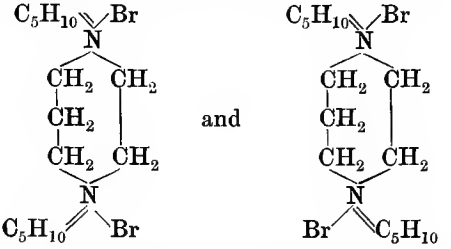
A further development is due to Aschan.[2] He acted (1) on ethylene dipiperide with trimethylene bromide and (2) on trimethylene dipiperide with ethylene dibromide. The products, which must both be ethylene-trimethylene-dipiperidinium bromide:—



[1] *Ber.* **41**. 3966 (1908).

[2] *Z. Ph. Ch.* **46**. 293 (1903).

were found to possess different physical properties, and neither of them could be separated into active forms. This is most easily explained as a case of cis-trans-isomerism, like that of the hexahydro-terephthalic acids:—



The various stereo-formulae which have been proposed for the pentavalent nitrogen atom are still too doubtful to be worth discussing. We must content ourselves at present with observing the facts: which are, to put them briefly, that a nitrogen atom with five different groups can exist in two optically active forms, and offers in general the same possibilities of isomerism as a carbon atom with four different groups. Inactive isomers cannot be produced unless there are two such asymmetric nitrogen atoms: a difference in the order of introduction of the groups on a single nitrogen atom is not sufficient to cause isomerism.

On the other hand, as Meisenheimer's work shows, a nitrogen atom may be active when two of the groups attached to it are the same, if these are negative groups. To explain this, he assumes that four of the groups attached to a pentavalent nitrogen atom occupy positions analogous to the four groups on a carbon atom, allowing of two enantiomorphic arrangements when all four are different, while the fifth (ionizable) group is mobile, and takes up the preferential position determined by the other four. Thus stereoisomerism is possible if one of these four groups is the same as the ionizable group, as it is in his base, but not if two positive groups (hydrocarbon radicals) are identical, which also agrees with experience. On this view the two hydroxyl groups in $R_3N\langle^{OH}_{OH}$ would be different, and this may account for the fact that these bodies behave as monacid bases.[1]

SUBSTITUTED ALKYLAMINES

Various amines containing substituted alkyl groups exist, most of which are not of great importance. Thus instead of alkyl radicals we may have their chlorine substitution-products attached to the nitrogen. These bodies may be made in various ways. Thus γ-chloro-butylamine is got by the reduction of γ-chloro-butyronitrile:—

$$CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CN \longrightarrow CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2.$$

It is an unstable compound, which can only exist as a salt. When the free base is liberated it changes spontaneously into the hydrochloride of pyrrolidine (tetrahydro-pyrrol):—

$$\begin{matrix}CH_2{-}CH_2\\ |\\ CH_2{-}CH_2\end{matrix}\rangle NH{\cdot}HCl.$$

[1] For a case of optical activity due in part to a trivalent nitrogen atom see p. 116.

The hydroxy-derivatives (amino-alcohols) are of some interest. The most easily obtained are those *a*-compounds which have the OH and the NH_2 attached to the same terminal carbon atom. These are the aldehyde-ammonias. They are formed by most (not all) fatty aldehydes with great ease: with the lower members by passing ammonia gas into the ethereal solution of the aldehyde, with the higher by treating the aldehyde with aqueous ammonia. It is to be noticed that the ketones do not give such compounds: in fact their formation depends on the presence of a CHO group attached to a primary alkyl radical:—

$$CH_3{\cdot}C\begin{matrix}H\\ \diagdown\!\!\diagup\\ O\end{matrix} + NH_3 = CH_3{\cdot}\overset{\displaystyle H}{\underset{\displaystyle NH_2}{C}}{\cdot}OH.$$

They split off the nitrogen as ammonia with remarkable ease in presence of dilute acids, re-forming the aldehydes. They can be reduced to alkyl-amines, and they polymerize readily. Thus ordinary aldehyde-ammonia when exposed to the air forms a substance resembling aldehyde resin.

The other oxy-amines, which have the OH and the NH_2 on different carbon atoms, are sharply distinguished from the aldehyde-ammonias by the fact that the nitrogen is firmly attached. They are strong stable bases. They are of interest from their close relationship to certain natural products. The dialkyl-amino-alcohols[1] and their esters are powerful anaesthetics.

The amino-alcohols are formed:—

(1) By the action of hal-hydrines such as glycol chlorhydrine on ammonia:—

$$CH_2OH{\cdot}CH_2Cl + NH_3 = CH_2OH{\cdot}CH_2NH_2 + HCl.$$

This reaction of course gives rise to all four classes.

(2) By the action of ammonia on the alkylene oxides:—

$$\begin{matrix}O\\ \diagup\!\!\diagdown\\ CH_2{-}CH_2\end{matrix} + NH_3 = HOCH_2{\cdot}CH_2NH_2.$$

This reaction gives the primary, secondary, and tertiary bases.

(3) By Gabriel's phthalimide reaction. Thus potassium phthalimide and ethylene dibromide give $C_6H_4\begin{matrix}CO\\ \diagdown\!\!\diagup\\ CO\end{matrix}N{\cdot}CH_2{\cdot}CH_2{\cdot}Br$, and when this is heated with dilute sulphuric acid to 200–220° phthalic acid is split off, and at the same time the bromine is replaced by hydroxyl, giving $CH_2OH{\cdot}CH_2NH_2$.

This body $CH_2OH{\cdot}CH_2NH_2$, oxyethylamine, amino-alcohol, or ethanolamine, is best obtained by the action of ethylene oxide on strong ammonia. It is remarkable[2] for its volatility. The reaction-mixture can be separated completely by fractionation into water and the primary, secondary, and tertiary bases:—

$$HOCH_2{\cdot}CH_2NH_2,\ (HOCH_2{\cdot}CH_2)_2NH,\ (HOCH_2{\cdot}CH_2)_3N.$$

Ethanolamine is a colourless viscous liquid, of strong alkaline reaction, which boils at 171°. It absorbs carbon dioxide from the air, and forms stable salts. It is the mother substance of choline:—

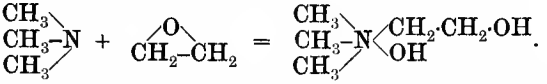
$$\begin{matrix}CH_3\\ CH_3{-}N\\ CH_3\end{matrix}\begin{matrix}\diagup\\ \diagdown\end{matrix}\begin{matrix}CH_2{\cdot}CH_2OH\\ OH\end{matrix},$$

[1] *C.* **06.** ii. 471, 472, 932.

[2] Knorr, *Ber.* **30.** 909 (1897).

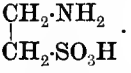
a product of the decomposition of lecithine. Lecithine is a compound of choline, glycerine-phosphoric acid, and stearic and palmitic acids, which is widely distributed in the animal and vegetable kingdoms, occurring in the brain, the nerves, in blood corpuscles, and in yolk of egg, as well as in the seeds of many plants.

The constitution of choline is shown by its synthesis from trimethylamine and ethylene oxide in concentrated aqueous solution :—

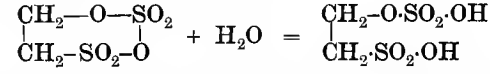


A more complicated substitution-product of ethylamine of some importance is taurine. It is the classical example of the danger of the method which is universally employed, of determining oxygen in organic analysis by difference. It is got from taurocholic acid, a substance occurring in various animal secretions. Taurine was discovered by Gmelin in 1824, and was supposed to be a compound of carbon, hydrogen, oxygen, and nitrogen, with the formula $C_2H_7NO_5$. Twenty-two years later Redtenbacher found that it contained sulphur, and determined its amount. It then appeared that its formula is $C_2H_7NSO_3$. But as the atomic weight of sulphur is nearly twice that of oxygen, the proportions of carbon, hydrogen, and nitrogen required by the two formulae are the same within the limits of experimental error.

The constitutional formula of taurine is :—

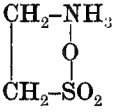


It is amino-ethyl sulphonic acid, as was shown by Kolbe, who synthesized it by the following method. When alcohol is treated with sulphur trioxide it gives 'carbyl sulphate', which is converted by cold water into ethionic acid, a sulphonic acid of ethyl sulphuric acid :—



When ethionic acid is boiled with water, the sulphuric acid group, being attached to carbon by the oxygen link, is split off, while the sulphonic group, being joined directly through sulphur, remains, and we get oxy-ethyl sulphonic acid, or isethionic acid, $CH_2OH{\cdot}CH_2{\cdot}SO_2{\cdot}OH$. When this is treated with phosphorus pentachloride, both hydroxyls are replaced by chlorine, but by the action of water on the product the acid chlorine is again replaced by hydroxyl, while the other chlorine is unaffected, giving chlorethyl sulphonic acid, $CH_2Cl{\cdot}CH_2{\cdot}SO_2{\cdot}OH$; and on heating this with ammonia, the chlorine is replaced by NH_2, to form amino-ethyl sulphonic acid, which is taurine.

An aqueous solution of taurine has a neutral reaction, obviously from the formation of an internal salt—



In the presence of metallic oxides it behaves as a weak acid and forms salts. It is reconverted by nitrous acid into isethionic acid.

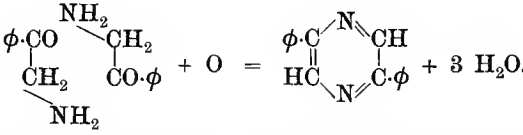
Amino-ketones

These bodies[1] can be made from the phthalimide derivatives of the fatty acids by acting on their chlorides with benzene and aluminium chloride, and saponifying the products:—

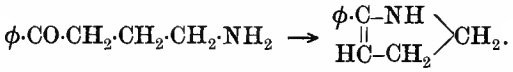
$$HO{\cdot}CO{\cdot}(CH_2)_n{\cdot}N\langle\begin{matrix}CO\\CO\end{matrix}\rangle C_6H_4 \longrightarrow Cl{\cdot}CO{\cdot}(CH_2)_n{\cdot}N\langle\begin{matrix}CO\\CO\end{matrix}\rangle C_6H_4$$

$$\longrightarrow \phi{\cdot}CO{\cdot}(CH_2)_n{\cdot}N\langle\begin{matrix}CO\\CO\end{matrix}\rangle C_6H_4 \longrightarrow \phi{\cdot}CO{\cdot}(CH_2)_n{\cdot}NH_2.$$

Their behaviour depends mainly on the distance between the amino-groups and the carbonyl. The α-compounds, such as amino-acetophenone $\phi{\cdot}CO{\cdot}CH_2{\cdot}NH_2$, are stable only as salts, and when set free oxidize spontaneously in the air to pyrazines:—



The β-compounds are stable. The γ- and δ- lose water as soon as they are set free, forming tetrahydro-pyrrols and tetrahydro-pyridines respectively: e. g.:—



But the corresponding formation of a 7-ring compound from ϵ-amino-caprophenone, $\phi{\cdot}CO{\cdot}(CH_2)_5{\cdot}NH_2$, does not take place. These reactions resemble those of the hydroxy-acids, and suggest that the amino-ketones are really enols, $\phi{\cdot}C(OH){:}CH{\cdot}(CH_2)_n{\cdot}NH_2$: a conclusion supported by the fact that many bodies of this class will form salts with alkalies, which are in some cases stable in aqueous solution.[2]

AMINO-ACIDS

The carboxyl derivatives of the alkylamines, the amino-acids, are of great importance from their close relationship to various products of organized life. They are found in the juices of plants and in animals, and constitute the greater part of the decomposition-products of albuminoid substances—white of egg, casein, blood-fibrin, silk, gelatine, &c.—whether by decay or by the action of acids or alkalies. It is therefore evident that they form constituent parts of the molecules of these bodies of fundamental physiological importance, the investigation of whose structure is one of the highest aims of organic chemistry.

For this reason the amino-acids have for a long time attracted a considerable amount of attention; and in particular since 1899 they have been studied in great detail by Emil Fischer, with his customary ingenuity and success. He has attacked the problem both from the analytical and from the synthetical

[1] Gabriel, *Ber.* **40.** 2649 (1907); **41.** 1127, 2010 (1908).

[2] Willstatter, Bode, *Ber.* **33.** 411; v. Miller, Rohde, ib. 3222 (1900); Rabe, Schneider, *Ber.* **41.** 872 (1908).

side. He has discovered new methods of synthesizing the amino-acids and of building up more complicated molecules from them, and at the same time he has greatly extended our knowledge of the decomposition-products of the proteins.

For their formation almost any of the regular methods for making amines can be used. The following are the most important:—

1. Gabriel's phthalimide reaction, using a halogen-substituted ester such as β-iodo-propionic, which gives β-amino-propionic acid:—

$$C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle N\cdot CH_2\cdot CH_2\cdot COOEt \longrightarrow H_2N\cdot CH_2\cdot CH_2\cdot COOH.$$

An important extension of this method has been made by Sörensen.[1] He treats potassium phthalimide with bromo-malonic ester, giving

$$C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle N-C\langle\begin{matrix}COOEt\\COOEt\end{matrix}\quad\text{(H)}.$$

The remaining hydrogen of the methylene group can then be replaced by sodium, and this, on treatment with alkyl halide, by alkyl. For example, with benzyl chloride the benzyl derivative is formed, and this on boiling with aqueous potash has the ester groups saponified and the ring broken, with the formation of the substituted phthalamic acid:—

$$C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle N-C\langle\begin{matrix}COOEt\\COOEt\end{matrix}\quad\text{($CH_2\cdot\phi$)} \longrightarrow C_6H_4\langle\begin{matrix}COOH\\CO\cdot NH\cdot C\langle\begin{matrix}COOH\\COOH\end{matrix}\quad\text{($CH_2\cdot\phi$)}\end{matrix}.$$

When this substance is heated with concentrated hydrochloric acid the amide is saponified, and at the same time one of the two α-carboxyls is split off, leaving in this case β-phenyl-α-amino-propionic acid or phenyl-alanine,

$$\phi CH_2\cdot CHNH_2\cdot COOH.$$

Since any required alkyl can be introduced into the malonic ester residue, this method enables us to prepare any mono-substituted glycollic acid.

2. Fischer has recently[2] developed a still simpler way of making the amino-acids through malonic acid. The required alkyl-malonic acid, $R\cdot CH(COOH)_2$, is brominated, which gives an almost quantitative yield of the mono-brom-derivative $R\cdot CBr(COOH)_2$. This loses CO_2 on heating, to form the α-brom-acid $R\cdot CHBr\cdot COOH$, which is converted into the α-amino-acid by ammonia.

3. From the keto-acids by conversion into oximes or hydrazones and reduction:—

$$>C=O \begin{matrix}\nearrow >C=NOH \longrightarrow >CH-NH_2\\ \searrow >C=N-NH\phi \longrightarrow >CH-NH_2 + H_2N\phi\end{matrix}.$$

4. By the reduction of nitrile-acids (Mendius reaction). An example of the combination of the last two methods is afforded by Fischer's synthesis of α–ϵ-diamino-caproic acid, which is identical with lysine, a product of the decomposition of proteins. Trimethylene chlorobromide, $CH_2Cl\cdot CH_2\cdot CH_2Br$,

[1] *C.* **03.** ii. 33.

[2] Fischer, Schmitz, *Ber.* **39.** 351 (1906).

when treated with potassium cyanide[1] under proper conditions yields g-chlorobutyronitrile (trimethylene cyanchloride), $CH_2Cl{\cdot}CH_2{\cdot}CH_2CN$. This condenses with sodium-malonic ester[2] to $CN{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH{\cdot}(COOEt)_2$. This was the body with which Fischer[3] started. Nitrous acid acts upon it to split off one carboxethyl group and form the isonitroso-compound (oxime), which is saponified and treated with sodium and alcohol. Both the cyanide and the oxime groups are thus reduced, giving α-ϵ-diamino-caproic acid:—

$$CN{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}C(NOH)COOEt \longrightarrow H_2NCH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH(NH_2){\cdot}COOH.$$

5. The α-amino-acids are got by the Strecker reaction, the action of ammonia on cyanhydrins, or of prussic acid on aldehyde-ammonias:—

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C\!<\!\begin{matrix}OH\\CN\end{matrix} + NH_3 = \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C\!<\!\begin{matrix}NH_2\\CN\end{matrix} + H_2O.$$

The amino-nitriles so formed give amino-acids on hydrolysis.

Fischer has shown that by starting with a hydroxy-aldehyde it is possible by this reaction to prepare the oxy-amino acids, which also occur among the decomposition-products of proteins. Thus from glycollic aldehyde, $CH_2OH{\cdot}CHO$, he prepared α-amino-β-oxy-propionic acid,[4] $CH_2OH{\cdot}CHNH_2{\cdot}COOH$, identical with serine, a product of the hydrolysis of silk. In the same way from arabinose,[5] $CH_2OH{\cdot}(CHOH)_3CHO$, he got the acid $CH_2OH{\cdot}(CHOH)_3{\cdot}CHNH_2{\cdot}COOH$, which on reduction gives its aldehyde, $CH_2OH{\cdot}(CHOH)_3{\cdot}CHNH_2{\cdot}CHO$,[6] identical with glucosamine, a body obtained from certain fungi.

The amino-acids are crystalline substances, generally easily soluble in water, but only slightly in alcohol and ether. If the NH_2 is in the α-position they have a sweet taste[7]; in the β-position this is very slight, in the γ it is absent. It is remarkable that their power of acting as foods for microscopic fungi[8] changes in a similar way, though in the opposite direction. Moulds grow well in solutions of γ-amino-acids, less well in β-, and hardly at all in α-.

They have singularly high melting-points, glycocoll, for example, melting above 220°. They form salts both with acids and bases. There is reason to think that the free acids exist only in the form of intramolecular salts such as

$$\begin{matrix}CH_2{-}NH_3\\|\quad\quad|\\O{=}C{-}{-}O\end{matrix}.$$

This structure is indicated by their neutral reaction, their high melting-points, and their insolubility in alcohol and ether. In the case of some of their derivatives an analogous structure can be proved. Thus betaine, which is trimethyl-glycocoll, and may have either of the two formulae

$$\begin{matrix}CH_2{-}N(CH_3)_2\\|\\CO{\cdot}OCH_3\end{matrix} \quad \text{or} \quad \begin{matrix}\quad\quad\quad CH_3\\CH_2{-}N{-}CH_3\\|\quad\quad|\quad\quad\backslash CH_3,\\O{=}C{-}{-}O\end{matrix}$$

[1] Gabriel, *Ber.* **23**. 1771 (1890).
[2] Blank, *Ber.* **25**. 3041 (1892).
[3] *C.* **02**. i. 985.
[4] *C.* **02**. i. 762.
[5] Fischer, Leuchs, *Ber.* **35**. 3787 (1902).
[6] *Ber.* **36**. 24 (1903).
[7] *Ber.* **35**. 2660 (1902).
[8] *Ber.* **35**. 2289.

is shown to have the second formula by the ease with which it splits off trimethylamine.

When heated with barium oxide the amino-acids split off CO_2 and form amines:— $CH_2NH_2{\cdot}COOH = CO_2 + CH_3NH_2$.

When the acids are treated with nitrous acid, the normal reaction of a primary alkylamine takes place, and the NH_2 is replaced by hydroxyl. But if their esters are treated with nitrous acid, by acting on the ester-hydrochloride with potassium nitrite, a so-called fatty diazo-compound is produced, which is not a true diazo-compound at all, but contains a ring of two nitrogen atoms and one carbon. Thus glycocoll yields diazo-acetic ester:—

$$\begin{matrix}CH_2{\cdot}NH_2\\ |\\ CO{\cdot}OC_2H_5\end{matrix} + O{=}NOH = \begin{matrix}HC\overset{N}{\diagdown\!\!\diagup}\!\!\underset{N}{\|}\\ |\\ CO{\cdot}OC_2H_5\end{matrix} + 2\,H_2O.$$

They are easily reduced by sodium amalgam to amino-aldehydes, the amino-group apparently promoting the reduction in the same way as the hydroxyl group in hydroxy-acids.[1]

As an example of the properties of an amino-acid we may take those of the simplest member of the series, glycocoll, glycine, or amino-acetic acid, $CH_2NH_2{\cdot}COOH$. It was originally obtained by hydrolysing glue with baryta or dilute sulphuric acid, whence the name (γλυκύς sweet and κόλλα glue). It occurs in nature as such, in mussels, more often in the form of derivatives, such as betaine, in sugar-beet and other plants, and hippuric acid, in the urine of herbivora. It is best obtained from hippuric acid (benzoyl-glycocoll), by hydrolysing it with dilute acid to benzoic acid and glycocoll:—

$$\phi{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}COOH + H_2O = \phi{\cdot}COOH + NH_2{\cdot}CH_2{\cdot}COOH.$$

It may also be obtained from chloracetic acid and ammonia, or, by Strecker's reaction, from formaldehyde, prussic acid, and ammonia:—

$$HC\overset{H}{\underset{O}{\diagdown\!\!\diagup}} + HCN \rightarrow H{\cdot}C\overset{H}{\underset{CN}{\diagdown\!\!\diagup}}OH \xrightarrow{(NH_3)} H{\cdot}C\overset{H}{\underset{CN}{\diagdown\!\!\diagup}}NH_2 \xrightarrow[\text{with BaO}]{\text{heated}} H{\cdot}C\overset{H}{\underset{COOH}{\diagdown\!\!\diagup}}NH_2.$$

It is also formed from cyanogen by the action of hydriodic acid, a peculiar reaction in which one CN group is reduced while the other is saponified:—

$$\begin{matrix}C{\equiv}N\\ |\\ C{\equiv}N\end{matrix} + 4\,HI + 2\,H_2O = \begin{matrix}CH_2{\cdot}NH_2\\ |\\ COOH\end{matrix} + 2\,I_2 + NH_3.$$

Glycocoll is a crystalline substance with a sweet taste. It turns brown at 228° and melts at 232–236°—nearly 220° higher than acetic acid.

If treated with alcohol and hydrochloric acid it is converted into its ethyl ester hydrochloride, $CH_2NH_3Cl{\cdot}COOEt$. This is a crystalline body melting at 144°, which can be sublimed by cautious heating. If it is treated with potassium nitrite in aqueous solution, diazoacetic ester, $CHN_2{\cdot}COOEt$, is precipitated as a yellow oil: this was the first known fatty diazo-compound, discovered by Curtius[2] in 1883. The intermediate nitrite of glycocoll ester, $CH_2(NH_3ONO)COOEt$, can be obtained by treating the hydrochloride suspended

[1] E. Fischer, *Ber.* **41**. 1019 (1908); cf. Neuberg, ib. 956.

[2] *Ber.* **16**. 2230.

in dry ether with silver nitrite. It is unstable, and readily loses water to give diazoacetic ester.

The hydrochloride of the ester when distilled with sodium carbonate undergoes a remarkable intramolecular change, giving propylamine:—

$$\begin{matrix}CH_2NH_2\\ |\\ CO\cdot OC_2H_5\end{matrix} = \begin{matrix}CH_2\cdot NH_2\\ |\\ C_2H_5\end{matrix} + CO_2.$$

This is analogous to the formation of stilbene on heating phenyl fumarate or phenyl cinnamate[1]:—

$$\begin{matrix}CH\cdot CO\cdot O\phi\\ \|\\ CH\cdot CO\cdot O\phi\end{matrix} = CO_2 + \begin{matrix}CH\cdot\phi\\ \|\\ CH\cdot CO\cdot O\phi\end{matrix} = 2\,CO_2 + \begin{matrix}CH\cdot\phi\\ \|\\ CH\cdot\phi\end{matrix}.$$

Free glycocoll ester is got from the hydrochloride by treatment with silver oxide, or more conveniently, as Fischer has shown, with strong aqueous soda at a low temperature. It is an unstable liquid, B. Pt. 148–9°, with a strong basic reaction. It decomposes spontaneously, and is saponified by water.

The polypeptides and the structure of the Proteins[2]

The main interest of the amino-acids arises from their relationship to the proteins. The proteins are an extremely important class of substances derived from living matter, and forming the chief constituents of protoplasm, as well as other animal and vegetable substances. They are very numerous, and are obtained from the most various sources; they include such bodies as gelatine, white of egg, casein (from milk), globulin (from blood serum), while others are got from horn, silk, and so forth. They are all decomposed by boiling with acids and in other ways, and by far the most important products of their decomposition are in all cases certain amino-acids. The first step towards the investigation of their structure is the separation and identification of the products of their hydrolysis. This is a work of unusual difficulty. An excessively complicated mixture of substances is obtained in every case (thus gelatine gives glycocoll, alanine, pyrrolidine-carboxylic acid, leucine, aspartic acid, glutamic acid, phenyl-alanine, amino-valeric and amino-butyric acids, together with oxy-amino- and diamino-acids and other substances). It is obviously not easy to separate and identify the constituents of such a mixture, many of them only occurring in very small quantity: and the difficulty is increased by the properties of the amino-acids, which are insoluble in ether, are soluble both in acids and alkalies, and have no definite melting-points. E. Fischer has, however, devised a method by which they can be separated with comparative ease, by making use of the fact that the esters of the amino-acids are volatile (at any rate under greatly reduced pressure) without decomposition, and that their boiling-points lie far apart. As this method has been of the utmost service we may consider in detail the separation of the products of the

[1] Anschütz, *Ber.* **18.** 1945 (1885).

[2] See the numerous papers of E. Fischer and his pupils in the *Berichte* from 1899 onwards, and in the *Zeitschr. f. physiologische Chemie* for the same years. Only the more important references are given in the text. Fischer has summed up the work up to the end of 1905 in a lecture, *Ber.* **39.** 530. Cf. also Kossel, *Ber.* **34.** 3214 (1901), and Cohen, *Organic Chemistry* (1907), chap. xi.

decomposition of casein, which is typical of the other bodies investigated. Casein is the protein of milk, and is made by precipitating milk with hydrochloric acid.

A kilogram[1] of casein was hydrolysed by prolonged boiling with pure concentrated hydrochloric acid. From the product the glutamic acid (α-aminoglutaric acid, $COOH{\cdot}CHNH_2{\cdot}CH_2{\cdot}CH_2{\cdot}COOH$) was separated as the slightly soluble hydrochloride. The residue, containing the amino-acids, was evaporated down, stirred up with absolute alcohol, and saturated with gaseous hydrochloric acid. This converts the amino-acids into their ethyl esters, which of course combine with the hydrochloric acid (owing to the presence of the NH_2) to form hydrochlorides. The product was then treated with excess of strong caustic soda to remove the hydrochloric acid and liberate the free esters. By keeping the temperature low saponification of the esters is avoided. The liquid was saturated with potassium carbonate to diminish the solubility of the esters, which can then be extracted with ether. The mixed esters were then fractionated under 8–15 mm. pressure, and thus separated into 8 fractions, boiling from 40° to 160°, of which the largest (165 gr. from 1 kgr. casein) boiled at 80–85°. For the further separation of the esters in each fraction it was saponified with baryta, and the amino-acids separated by means of their copper salts and in other ways.

This method has been applied with excellent results to the hydrolysis of a large number of similar substances, such as silk, white of egg, horn, gelatine, &c. In some cases it is necessary to conduct the distillation of the mixed esters at pressures not exceeding 1 mm. For this purpose the ordinary water-pump is quite useless, as it will not produce a higher vacuum than 10 to 15 mm.; and even a mercury-pump is not much good, because in such cases of the distillation of a mixture of substances, where there is always a certain amount of decomposition, the gases and volatile bodies so produced tend to increase the pressure. To avoid these difficulties Fischer[2] employs a powerful air-pump, such as is used for exhausting the globes of incandescent lamps, and interposes between the pump and the receiver a condenser cooled with liquid air, by which the more volatile decomposition-products are prevented from getting into the pump. By these means he is able to conduct the distillation under a pressure of a third of a mm. or less. The importance of this becomes evident when one considers that Krafft has found that a diminution of pressure from 15 mm. (the lowest that a water-pump ordinarily gives) to the vacuum of the cathode light ($\frac{1}{10}$ to $\frac{1}{40}$ mm.) lowers the boiling-point by 70–100 degrees.

A further difficulty in identifying the amino-acids obtained in this way from natural sources arises from the fact that they nearly all contain asymmetric carbon and occur in the active forms, whereas the synthetic substances with which they are compared are of course inactive, and are usually racemic compounds, so that their physical constants are different from those of the active modifications. For a satisfactory identification it is necessary to split the racemic form into its active components. This is not easy, because the moulds, as we have seen, do not as a rule grow easily in the solutions of these

[1] *C.* **01.** ii. 691.

[2] *Ber.* **35.** 2158 (1902).

acids, and their feebly basic and feebly acidic character makes it difficult to form their salts either with active acids or with active bases. Fischer finds [1] that by treating the amino-acids in alkaline solution with benzoyl chloride (Schotten-Baumann reaction) they give the much more acidic benzoyl derivatives (e. g. ϕ·CO·NH·CH_2·COOH) which form stable salts with active bases such as brucine, which can then be separated into their active forms by fractional crystallization. The corresponding formyl derivatives [2] are even better for this purpose, as they are more easily produced (merely by boiling the amino-acids with anhydrous formic acid) and are more easily saponified again after separation, so that there is no danger of racemization.

All the proteins give very similar products on hydrolysis. The most important are the following:—

Monamino-acids.

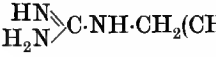
Glycine or glycocoll, α-amino-acetic acid, CH_2NH_2·COOH.
Alanine, α-amino-propionic acid, CH_3·CH_2NH_2·COOH.
Phenyl alanine, α-amino-β-phenyl-propionic acid, ϕCH_2·$CHNH_2$·COOH.
Valine, α-amino-isovaleric acid, $(CH_3)_2CH$·$CHNH_2$·COOH.
Leucine, α-amino-isocaproic acid, $(CH_3)_2CH$·CH_2·$CHNH_2$·COOH.
Aspartic acid, aminosuccinic acid, COOH·CH_2CHNH_2·COOH.
Glutamic acid, α-amino-glutaric, COOH·CH_2·CH_2·$CHNH_2$·COOH.

Hydroxy-amino-acids.

Serine, α-amino-β-hydroxy-propionic acid, CH_2OH·$CHNH_2$·COOH.
Isoserine, β-amino-α-hydroxy-propionic acid, CH_2NH_2·CHOH·COOH.
Tyrosine, α-amino-p-oxyphenyl-propionic acid, HOC_6H_4·CH_2·$CHNH_2$·COOH.

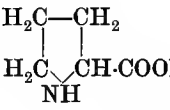
Diamino-acids.

Ornithine, α-δ-diamino-valeric acid, CH_2NH_2·$(CH_2)_2CHNH_2$·COOH.
Lysine, α-ϵ-diamino-caproic acid, $CH_2NH_2(CH_2)_3CHNH_2$·COOH.
Arginine, α-amino-δ-guanido-valeric acid,

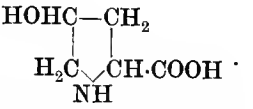


Heterocyclic compounds.

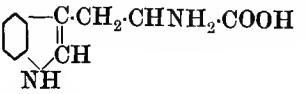
Proline, α-pyrrolidine-carboxylic acid,



Oxyproline, hydroxy-pyrrolidine-carboxylic acid,



Tryptophane, indole-aminopropionic acid,



[1] *Ber.* **32.** 2451, 3638 (1899); **33.** 2370 (1900).
[2] Fischer, Warburg, *Ber.* **38.** 3997 (1905).

There are also one or two sulphur compounds, such as cystine, α-amino-β-thiolactic acid, $CH_2SH{\cdot}CHNH_2{\cdot}COOH$, which is the sulphur analogue of serine. The occurrence of the two pyrrolidine derivatives is remarkable, especially as they are found to be present in almost all proteins. It is possible that they are only produced by secondary reactions, as they have an obvious relation to amino-acids: thus proline would be produced by the loss of water from α-amino-δ-oxy-valeric acid,

$$\begin{array}{l} CH_2\text{–}CH{\cdot}COOH \\ \quad\quad\quad\quad\ \diagdown NH_2 \\ CH_2{\cdot}CH_2OH \end{array},$$

but there is reason to think that this is not the case. It is especially to be noticed that with the single exception of isoserine, all these bodies are α-amino-acids, or are simply derived from them.

Since the proteins are so readily split up into these acids, it is natural to expect that we may be able to build up the proteins from them. It is to this end that the second part of Fischer's work is directed. We can hardly expect to be able at first to form the proteins themselves; for they are the most complicated compounds of the whole group, and have molecular weights which are supposed to be about 15,000, and are certainly enormous. We should rather try to meet the synthesis half-way, so to speak, and to build up some of the simpler earlier decomposition-products of the proteins. Such bodies are the peptones. They are the simplest products of the hydrolysis of the proteins by the gastric juice and certain other enzymes. They resemble the proteins in general behaviour, but are very soluble in water, acids, and alkalies, and are not coagulated by the ordinary methods. They have molecular weights of about 600—that is to say high, but not excessively so. They have an obviously close relationship to the proteins from which they are produced, and to the amino-acids into which they are converted by further hydrolysis. The problem which Fischer set himself was the formation of bodies resembling the peptones from the α-amino acids. Now it has long been known[1] that these acids can be converted into complex substances of high molecular weight. Thus glycocoll when heated with glycerine gives a so-called anhydride, resembling horn: and there are many other such cases. But the products are always amorphous bodies of indefinite character: the 'brutal' reactions, as Fischer calls them, by which they are produced throw no light on their structure: and nothing is known as to their relationship to the natural proteins. It is clear that the only way of arriving at certain results is to discover methods by which the molecules of various amino-acids can be linked up together in successive stages to definite chemical individuals, whose structure can be satisfactorily determined.

As to the nature of the linkage there can be little doubt. It must be formed by loss of water, and it must be easily broken up again by hydrolysis, under the influence of mineral acids. This indicates that the bodies are of the nature of amides. Two molecules of amino-acid can obviously form an amide, which will still have a carboxyl group at one end, and an NH_2 at the other; so that the product can again form an amide with itself, or with another molecule

[1] Cf. Fischer, *Ber.* **34.** 2868 (1901).

of amino-acid. In fact, as far as the formulae go, there is no limit to the process; molecules of any size can be built up, with the general formula $R{\cdot}CHNH_2{\cdot}CO(NH{\cdot}CHR{\cdot}CO)_n{\cdot}NH{\cdot}CHR{\cdot}COOH$. To bodies of this type Fischer has given the name of polypeptides. He has worked throughout on the idea, which all his discoveries have confirmed, that the natural peptones are really mixtures of polypeptides. He has elaborated a series of methods for their synthesis, of which the most important are the following.

The α-amino-acids, and still more easily their esters, can be made to give bimolecular anhydrides analogous to glycide, the anhydride of glycollic acid. Thus glycine yields glycine anhydride, which has been shown to be a piperazine derivative, diketo-piperazine, of the formula $\begin{matrix} NH{\cdot}CH_2{\cdot}CO \\ | \quad\quad | \\ CO{\cdot}CH_2{\cdot}NH \end{matrix}$. It is, in fact, an intramolecular double amide. If this is treated with hydrochloric acid (or more conveniently with alkali [1]), it takes up water and the ring is broken, with the formation of the simple anhydride, $NH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}COOH$, which may be called glycyl-glycine, and is the simplest polypeptide. In this way the dipeptide of an amino-acid can be made, but for the further lengthening of the chain other methods have to be used. One of these is to treat the dipeptide with α-chloracyl chloride, which can be obtained by the Zelinsky method of chlorinating (or brominating) the acid in the presence of phosphorus. This adds on the chloracyl group to the NH_2. For instance, glycyl-glycine with chloracetyl chloride gives $CH_2Cl{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}COOH$, and when this is treated with ammonia the chlorine is replaced by NH_2, giving diglycyl-glycine, $NH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}COOH$. This can then be combined with chloracetyl chloride again, and a fourth glycyl group introduced, and so on.

Fischer has subsequently improved this method by the discovery [2] that the amino-acids themselves can be converted into their acid chlorides, $R{\cdot}CH(NH_3Cl)COCl$, by the action of phosphorus pentachloride in acetyl chloride solution. This reaction cannot be applied to the polypeptides themselves, but their chlor- or bromacyl derivatives, like the chloracetyl derivative of glycyl-glycine mentioned above, give acid chlorides in this way, and these of course condense with the NH_2 of a polypeptide, whereby the process of building up long chains is considerably simplified.

For the sake of simplicity, the glycine compounds have been used as examples of these synthetical methods; but Fischer's work has been extended to a large number of other naturally occurring amino-acids, and in this way he has produced more than a hundred polypeptides, of the most various kinds. The largest hitherto prepared is an octodeca-peptide, containing eighteen amino-acid residues.[3] Its name is l-leucyl-triglycyl-l-leucyl-triglycyl-l-leucyl-octoglycyl-glycine, its formula is

$NH_2CH(C_4H_9)CO{\cdot}(NH{\cdot}CH_2{\cdot}CO)_3{\cdot}NH{\cdot}CH(C_4H_9)CO(NH{\cdot}CH_2{\cdot}CO)_3NH{\cdot}CH(C_4H_9)CO(NH{\cdot}CH_2{\cdot}CO)_8{\cdot}NH{\cdot}CH_2{\cdot}COOH$, $(C_{48}H_{80}O_{19}N_{18})$,

and its molecular weight 1213. It is the compound of largest molecular

[1] *Ber.* **38.** 607 (1905). [2] *Ber.* **38.** 2917 (1905).
[3] *Ber.* **40.** 489 (1907).

weight known, whose constitution is definitely ascertained. It is soluble in 100 parts of water, and very easily in strong acids.

If Fischer's view as to the structure of the peptones is correct, these higher polypeptides ought to resemble them in properties: and to a very great extent this is the case. The typical reactions of the peptones are the biuret reaction, the formation of a red colour with potash and copper sulphate: the precipitation by phosphotungstic acid: and the hydrolysis to amino-acids by trypsin, the pancreatic ferment. All these reactions are given by many of the higher polypeptides. At the same time we must remember how extremely complicated the question is. It is probable that none of the natural peptones are single chemical individuals: many of them are no doubt mixtures of a great many compounds. But apart from this, the pure peptones must each be made up of ten or more residues of several different amino-acids, and we do not yet know at all exactly the proportions of these different acids which go to make up their structure, still less the order in which they are put together: and yet these two factors must have a profound influence on the properties of the product. It is to be hoped that by the study of a large number of polypeptides we may get some guiding principles as to the relations between their structure and their properties: but this must be a matter of time. Some indications have already appeared. Fischer and Abderhalden have shown that the susceptibility to ferments is much greater if the bodies are composed of the naturally occurring stereo-forms of the amino-acids. It also seems that the solubility, which is generally less with the artificial polypeptides than with the natural peptones, is increased with the use of the active modifications, with the employment of a variety of different amino-acids, and after reaching a minimum with an increasing length of chain, begins to increase again.

One of the most hopeful signs for the success of this investigation is the recent discovery that polypeptides identical with those prepared synthetically occur among the products of the hydrolysis of the natural proteins under suitable conditions. Thus fibroin [1] (from silk) gives glycyl-d-alanine, as well as a tetra-peptide, composed of two glycine molecules, one of d-alanine, and one of l-tyrosine; and there are several other similar cases.[2] This makes it practically certain that structures of the polypeptide type form part of the protein molecule; though it is not proved that they are wholly built up on this type. Fischer suggests that the piperazine ring (of the double anhydrides) may be present, and also that the hydroxyl groups of the oxy-amino-acids may play a part in the formation of the molecule. All these questions can only be settled by much further investigation.

BENZYLAMINE BASES

This group consists of those aromatic derivatives which have the amino-group in the side chain. They are prepared by the same methods as the fatty amines: by the action of ammonia on the halides, by the saponification of

[1] Abderhalden, *Ber.* **39.** 752, 2315 (1906); *C.* **07.** ii. 1533.

[2] Cf. Hougounenq, Morel, *Bull. Soc.* [4] **3.** 1146; *C. R.* **148.** 236 (1909); Abderhalden, *C.* **09.** i. 1246: ii. 1754.

isocyanates, by Gabriel's phthalimide reaction, &c. They may also be got by the reduction of the nitriles, which is often most conveniently carried out by combining them with hydrogen sulphide to the thio-amides, and then reducing these, which gives the amine and hydrogen sulphide:—

$$\phi\cdot CN \longrightarrow \phi\cdot CS\cdot NH_2 \longrightarrow \phi\cdot CH_2\cdot NH_2 + H_2S.$$

In general properties they closely resemble the alkylamines. They have a smell like that of ammonia, and are easily soluble in water. The aqueous solution has an alkaline reaction and absorbs carbon dioxide from the air. Like the alkylamines they give alcohols with nitrous acid, and not diazo-compounds, and with carbon bisulphide they form dithiocarbamates.

The acidic phenyl group exerts an influence on their basicity, though from its greater distance much less than in aniline. Thus the (apparent) strength of benzylamine is about equal to that of ammonia, that is to say much less than that of methylamine, but more than that of aniline.

CHAPTER III

AROMATIC AMINES

THE aromatic amines properly so called are those bodies in which the amino-group is directly attached to the benzene nucleus. They are formed by the reduction of nitro-compounds, and as the latter are easily obtained by direct nitration, the aromatic amines are much more accessible than the fatty, and in consequence are far better known. Indeed there is scarcely any class of bodies which has been investigated with so much industry and so much success. This work has of course been stimulated in no small degree by the value of the aniline derivatives as dyes.

The basis of our knowledge of aniline and its allies was laid down by Hofmann in 1846–1851 in his 'Contributions to our knowledge of the Volatile Organic Bases'.[1] 'Considering the very modest means which were then at the disposal of the organic chemist, and moreover that he was not able to obtain benzene, much less aniline, as a commercial product, it is astounding what an immense number of facts Hofmann discovered which are still amongst the most important in the whole subject.'[2]

The simplest of the aromatic amines, aniline, is also the most important. Thousands of kilograms of it are made in the great German factories every day. The annual production of aniline and similar bases in 1892 was 8,000 tons.

Aniline was first obtained by Unverdorben in 1826 by the distillation of indigo. In 1840 Fritzsche prepared it by distilling indigo with potash, and called it aniline from *añil*, the Spanish word for indigo. In 1843 Hofmann showed that this base obtained from indigo was identical with that which Runge in 1834 had found in coal tar, and with that which Zinin[3] had obtained in 1842 by the reduction of nitrobenzene. This last method of preparation proves its formula.

Aniline only occurs in very small quantity in coal tar, so this source, which was at first adopted, was very soon abandoned in favour of the reduction of nitrobenzene, which is now the sole method of preparation employed.

As reducing agents several substances have been adopted. Zinin used an alcoholic solution of ammonium sulphide, which is still used in certain cases, where we want to reduce one only of several nitro-groups. The reducing agent used in commerce is iron in presence of hydrochloric, or in more recent times of acetic acid. It is not necessary to take more than 5 per cent. of the calculated quantity of acid in either case. With hydrochloric acid it appears that ferrous chloride is formed, which then acts as a hydrogen carrier, so to speak, the rest of the iron being converted into ferric hydrate. With acetic

[1] *Ann.* **57–79.** [2] Meyer, Jacobson, *Lehrb.* ii. 172. [3] *Ann.* **44.** 286.

acid the iron forms ferric acetate, and the hydrogen evolved reduces some of the nitrobenzene to aniline; but at the high temperature employed (the mixture is heated with steam) the salt breaks up into ferric hydrate which is precipitated, and acetic acid which serves to dissolve more iron. In either case the reaction may be represented as consisting only in the oxidation of the iron to ferric hydrate and the simultaneous reduction of the nitrobenzene to aniline:—

$$2\,Fe + \phi NO_2 + 4\,H_2O = 2\,Fe(OH)_3 + \phi NH_2.$$

When the reaction is finished, the liquid is neutralized with lime and distilled with steam. The aniline, which forms the lower layer of the distillate, is run off, and the upper layer, consisting of an aqueous solution of aniline, is used to feed the boilers which supply the steam for further distillations.

In the laboratory the reduction is generally done with tin or stannous chloride, in presence of excess of strong hydrochloric acid.

Other methods for preparing aromatic amines are:—

(2) Heating the halogen derivatives of the aromatic hydrocarbons with the compound of calcium chloride and ammonia. This requires a very high temperature (360–370°), and gives a bad yield, owing to the firmness with which the halogens are attached to the benzene nucleus.[1] If there are nitro-groups on the same nucleus in the ortho or para position to the halogen, the reaction goes much more easily. Nitro-groups in the meta position have not this effect.

(3) By heating the phenols with the compound of zinc chloride and ammonia or with ammonium chloride to above 300°. In the case of certain negatively substituted naphthols it is found that their ethers react quite easily at moderate temperatures with alkylamines to form substituted naphthylamines[2]: for example:—

$$C_{10}H_5NO_2Br{\cdot}OEt + EtNH_2 = C_{10}H_5NO_2Br{\cdot}NHEt + HOEt.$$

This resembles the formation of amides from the esters and the amines, and is an example of the analogy between the phenols and naphthols and the acids.

Freshly prepared aniline is a colourless oily liquid, which soon turns reddish brown when exposed to the air: but this depends on the formation of very small quantities of oxidation-products, which may be removed by treatment with acetone, with which they combine.[3] If perfectly pure, aniline remains colourless even when exposed to the air for a long time. It melts at −8°, and boils at 183–184°. At 25° it dissolves 5 per cent. of water: while water at 16° dissolves 3 per cent. of aniline. It is easily soluble in the aqueous solution of its hydrochloride.

Many of its properties are identical with those of the alkylamines: but in many important points its behaviour is different. In particular its basicity is weakened by the acidic character of the phenyl group, which is also shown, for example, in the comparison of phenol and alcohol. It dissolves in mineral

[1] A lower temperature is sufficient, and a much better yield obtained, if the haloid compound is heated with ammonia under pressure, in presence of a copper salt. *C.* **08**. ii. 1221; **09**. i. 475, 600.

[2] Meldola, *J. C. S.* **1906**. 1434.

[3] Cf. Hantzsch, Freese, *Ber.* **27**. 2966 (1894).

acids (and also in organic acids) to form stable salts such as $\phi\cdot NH_3Cl$. But in contrast to the fatty amines it has no alkaline reaction to litmus or phenolphthalein: it cannot absorb carbon dioxide: and its mineral acid salts have an acid reaction. It is, however, sufficiently basic to precipitate the hydroxides of zinc, aluminium, and ferric iron from solutions of their salts.

It may be detected by giving a deep bluish violet with bleaching powder, and a fine blue colour with potassium bichromate in presence of strong sulphuric acid.

The aromatic amines, like the fatty, can have the hydrogen attached to nitrogen replaced by alkali metals, and by alkyl, aryl, or acyl groups. Sodium and potassium dissolve in hot aniline with evolution of hydrogen, to give compounds like $\phi\cdot NHK$ and $\phi\cdot NK_2$. Other such derivatives will be described later.

One of the most characteristic differences between the aromatic and the fatty amines is that the aromatic with nitrous acid give the diazo-compounds:—

$$\phi\cdot NH_2 + ONOH = H_2O + \phi\cdot N_2OH.$$

The diazo-compounds are of the utmost importance, both theoretical and practical. They are capable of more varied reactions than almost any other class of bodies, and they form an intermediate stage in the preparation of by far the greater number of aniline dyes. Moreover they have given rise to a series of investigations which have been of the highest value in extending our knowledge of the phenomena of tautomerism.

The characteristic reaction of the primary alkylamines with nitrous acid (giving nitrogen and the alcohol) occurs also with the aromatic amines, the diazo-compounds breaking on warming with the greatest ease to give phenols, with evolution of nitrogen.

This formation of diazo-compounds gives us a means of determining nitrous acid volumetrically.[1] The nitrous acid solution is titrated against aniline hydrochloride solution at $-10°$, potassium iodide and starch being used as indicator. As long as aniline is present, the nitrous acid is all used up in diazotizing it; but as soon as it is gone, the iodine is liberated and colours the starch blue. The strength of the aniline solution is determined by titrating it under the same conditions against potassium nitrite.

Another reaction characteristic of the aromatic amines is with carbon bisulphide. The alkylamines react with it very readily in the cold to give dithiocarbamic salts:—

$$\begin{matrix} CH_3NH_2 \\ CH_3NH_2 \end{matrix} + \begin{matrix} C{=}S \\ \| \\ S \end{matrix} = \begin{matrix} CH_3N\langle^{H}_{C{=}S} \\ CH_3NH_3{-}S\rangle \end{matrix}.$$

The aromatic amines do not as a rule react in the cold at all. They do so, however, readily on heating, but then they split off hydrogen sulphide, and form disubstituted thioureas:—

$$\begin{matrix} \phi\cdot N\langle^{H}_{H} \\ \phi\cdot N\langle^{H}_{H} \end{matrix} + S{=}C{=}S = \begin{matrix} \phi\cdot N\langle^{H}_{C{=}S} \\ \phi\cdot N\langle^{H}_{H} \end{matrix} + H_2S,$$

[1] Vignon, Bay, *C. R.* **135**. 507; *C.* **02**. ii. 1094.

the product in this case being generally known as thiocarbanilide. The reaction is greatly hastened by dissolving a small quantity of sulphur in the mixture: but how this acts is not known.

The aromatic amines have a curious reaction with sulphurous acid.[1] If they are treated with sodium hydrogen sulphite ammonia is expelled, and an acid sulphite (not sulphonate) is formed:—

$$R{\cdot}NH_2 + NaHSO_3 = R{\cdot}O{\cdot}SO_2Na + NH_3.$$

These acid sulphites are readily saponified (e. g. by alkalies) to the corresponding phenols, which shows that the sulphur is attached to carbon through oxygen. Conversely, the phenols are converted into amines by treatment with ammonium sulphite and ammonia, no doubt with intermediate formation of the sulphite esters, so that the reaction is reversible throughout:—

$$\text{Amine} \underset{NH_3}{\overset{\text{Bisulphite}}{\rightleftharpoons}} \text{Ester} \underset{NaHSO_3}{\overset{\text{Alkali}}{\rightleftharpoons}} \text{Phenol.}$$

Fatty amines and alcohols do not give these reactions at all; and even the benzene derivatives do so much less readily than those of naphthalene.

Aniline is very susceptible to oxidation and gives various products, which will be discussed later, in dealing with the general question of the oxidation of amines.

On the other hand it resists reducing agents strongly, as is shown by its ready formation from nitrobenzene. It cannot be converted into its hexahydro-compound, though this body exists and can be prepared by indirect methods.

SUBSTITUTED ANILINES

The very numerous substitution-products of aniline fall into two main divisions:—

A. Those in which the hydrogen of the NH_2 is replaced: these again are divided into

1. The alkyl substitution-products (mixed amines).
2. The aryl substitution-products (purely aromatic amines).
3. (The acyl-anilines: these are amides, and as such will be considered later.)

B. Those in which the hydrogen attached to the nucleus is replaced.

A. 1. The mixed alkyl-aryl-amines may be secondary, tertiary, or quaternary. They are made as in the fatty series by heating aniline with the alkyl halides: commercially by heating it in an autoclave with the necessary alcohol and hydrochloric or sulphuric acid to 180–200°, when the nascent alkyl ester reacts. In this way the tertiary mixed amines, such as dimethyl-aniline, can be got in the pure state, but not the secondary, as even if the calculated quantities are used, some tertiary amine is formed, and some aniline is not acted on. Hence to isolate the secondary compound some method of separation must be adopted. The simplest is by means of nitrous acid. The mixed bases are treated at a low temperature in hydrochloric acid solution with sodium

[1] Bucherer, *J. pr. Ch.* [2].**69**. 49 (*C.* **04**. i. 811).

nitrite. The primary base gives a diazonium chloride, which is soluble in the acid liquid: the tertiary gives the hydrochloride of the nitroso-derivative, $ON{\cdot}C_6H_4{\cdot}NR_2HCl$, which is also soluble. The secondary gives, as an alkylamine would, a true nitrosamine, $\phi{\cdot}NR{\cdot}NO$, which, being no longer basic, is insoluble. This is separated and reduced, whereby the nitroso-group is removed, and the secondary amine $\phi NH{\cdot}R$ is re-generated.

Owing to this difficulty it is often better to use an indirect method of preparation for the secondary amines. Thus the sodium derivative of acetanilide has the sodium replaced by alkyl on treatment with alkyl halide, and the acetyl group can be split off from the product by boiling with potash:—

$$\phi{\cdot}N\langle^{CO{\cdot}CH_3}_{Na} \rightarrow \phi{\cdot}N\langle^{CO{\cdot}CH_3}_{Alk} \rightarrow \phi{\cdot}N\langle^{H}_{Alk} + CH_3{\cdot}COOH.$$

There are various other methods of alkylation, among which the introduction of methyl groups by means of formaldehyde may be mentioned. Formaldehyde combines[1] with aniline to give the so-called anhydro-formaldehyde-aniline, $\phi{\cdot}N{=}CH_2$, which is reduced by tin and hydrochloric acid to mono-methyl-aniline, $\phi{\cdot}NH{\cdot}CH_3$. This again combines with formaldehyde in hydrochloric acid solution to give $\phi{\cdot}N(CH_3)CH_2Cl$, which is converted by reduction into dimethyl-aniline. In some cases[2] it is sufficient to heat the hydrochloride of the base with formaldehyde alone to 120-160° under pressure; the aldehyde acts as its own reducing agent, being partly oxidized to carbon dioxide and partly reduced to methyl alcohol. (Compare the analogous behaviour of benzaldehyde in presence of alkali, giving its acid and its alcohol.)

The secondary and tertiary mixed amines are oily liquids, which distil unchanged. They have no alkaline reaction, as the influence of the phenyl group still outweighs that of the alkyl. They give salts with one equivalent of acid, and have many of the properties of the purely fatty compounds.

Many tertiary mixed amines differ from the tertiary alkylamines in reacting with extraordinary ease with nitrous acid. They have of course no hydrogen on the nitrogen to go out with the hydroxyl of the nitrous acid: but the presence of the dialkyl-amino-group renders the para hydrogen on the benzene nucleus sufficiently mobile to react.

$$(CH_3)_2N\langle\rangle H + HO{\cdot}NO = H_2O + (CH_3)_2N\langle\rangle NO.$$

There are many other instances in which this para hydrogen atom shows itself to be extremely reactive: it can combine with many bodies which do not react with benzene itself. Thus with benzaldehyde it gives malachite green

$$\phi{\cdot}CHO + 2\,H\langle\rangle N(CH_3)_2 = \phi{\cdot}CH[-\langle\rangle N(CH_3)_2]_2 + H_2O.$$

This reaction can be made to take place with benzene, but less easily.

With carbonyl chloride it gives a ketone (Michler's ketone)

$$CO{\cdot}Cl_2 + 2\,H{-}\langle\rangle{-}N(CH_3)_2 = CO[-\langle\rangle N(CH_3)_2]_2 + 2\,HCl.$$

In the same way it will condense[3] through the para hydrogen with oxalic ester and with ketones.

The hydrochlorides of the mixed amines undergo a remarkable change on

[1] C. Goldschmidt, *C.* **05.** i. 227.

[2] Eschweiler, *Ber.* **38.** 880; Koeppen, *Ber.* **38.** 882 (1905).

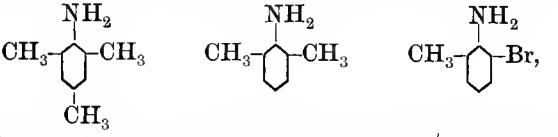
[3] Guyot, *C. R.* **144.** 1051 (1907); Guyot, Haller, ib. 947.

heating, which was discovered by Hofmann. If they are heated in an open tube in a current of hydrochloric acid gas, the alkyls are split off as halides: thus the final products of the action of hydrochloric acid on dimethyl-aniline are aniline hydrochloride and methyl chloride. But if the salt is heated alone in a tube to 300°, though this decomposition may very likely occur first, the reaction goes further and the alkyl is replaced: not, however, on the nitrogen, but on the nucleus. Thus:—

$$C_6H_5{\cdot}NHC_2H_5{\cdot}HCl = C_6H_4\begin{matrix}C_2H_5\\NH_2\end{matrix}{\cdot}HCl.$$

The most important of these mixed amines is dimethyl-aniline, the mother substance of a whole series of valuable dyes, such as auramine, crystal-violet, methylene blue, malachite green, &c. It has an extraordinary power of forming condensation-products, owing to the mobility of the para hydrogen. Thus if it is gently oxidized, for example, with chloranil (tetrachloro-quinone, $C_6Cl_4O_2$) or copper chloride, it is converted into methyl violet, a mixture of the hydrochlorides of the penta and hexa-methyl derivatives of triamino-triphenyl-carbinol, $HO{\cdot}C(C_6H_4NH_2)_3$. The linking methane carbon undoubtedly comes from the separation of one of the methyl groups as formaldehyde. If manganese dioxide and sulphuric acid are used as the oxidizing agents, formaldehyde can actually be detected.

The quaternary halides are got from the tertiary bases by the action of alkyl halide. But this reaction sometimes occurs with great difficulty, and sometimes not at all. Thus Fischer[1] has shown that anilines in which both the ortho-positions to the nitrogen are replaced, such as



though they form tertiary bases easily, will not form quaternary compounds at all. This is obviously a case of stereo-hindrance, and is analogous to the inactivity of the di-ortho-substituted benzoic acids and their esters, acid chlorides, amides, and nitriles.

When the quaternary salts are heated above 300°, the alkyl groups, as has been mentioned, migrate to the ring, occupying first the ortho positions, and then the para. Thus trimethyl-phenyl-ammonium iodide, $\phi{\cdot}NMe_3I$, gives dimethyl-toluidine, methyl-xylidine, and finally symmetrical amino-trimethyl-benzene, or mesidine.

The quaternary hydroxides, unlike the primary, secondary, and tertiary bases, are strongly basic caustic substances.

A. II. *Purely aromatic amines*

Diphenylamine, $N\phi_2H$, was discovered by Hofmann in 1864. It is of commercial importance as the source of certain dyes. It is made by heating aniline with its hydrochloride to 200°.

$$\phi NH_2 + \phi NH_3Cl = \phi_2NH + NH_4Cl.$$

[1] *Ber.* **33.** 345, 1967 (1900).

It can also be made by heating the phenols with aniline in the presence of zinc chloride, calcium chloride, or antimony trichloride. This latter method is useful for preparing unsymmetrical secondary amines, with substituted nuclei.

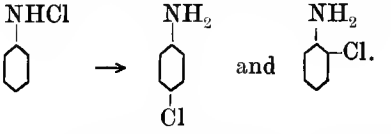
Diphenylamine melts at 54° and boils at 302°. It is scarcely soluble in water. Its basic character is much weakened by the presence of the second phenyl group; it gives salts with strong acids, but they are at once decomposed by water.

Its solution in concentrated sulphuric acid gives a deep blue colour in presence of a trace of nitric acid, which affords a very delicate test for the latter. It has been shown[1] that this reaction is due to the formation of tetraphenyl-hydrazine, $\phi_2N{\cdot}N\phi_2$, by the oxidation of the diphenylamine.

The purely aromatic tertiary amines are difficult to prepare and are little known. Triphenylamine, $N\phi_3$, is got by dissolving sodium in boiling diphenylamine and treating the product with phenyl bromide. It is not a base at all. It gives no salt with hydrochloric acid even when the gas is passed into its benzene solution. This is a remarkable proof of the negative nature of the phenyl group as compared with alkyl. If we replace the hydrogen of ammonia by alkyl groups, we get a strong base, which is stronger the more alkyls it contains: while the introduction of aryl (e.g. phenyl) groups produces a continuous diminution of the basic character. Phenylamine (aniline) has no alkaline reaction and does not absorb carbon dioxide: diphenylamine gives salts only with strong acids, and these are decomposed by water: triphenylamine gives no salts at all.

B. *Aniline derivatives substituted in the nucleus*

These may be obtained by direct substitution, or in other ways. When they are obtained by direct substitution, the substituents occupy the ortho and para positions, in accordance with Crum Brown's rule. (In some cases, where the reaction is carried on in strong acid solution, the meta position is taken up as well: this must be due to the fact that it is not the aniline which is then being substituted, but its salt.) It is to be observed that in many cases of the direct substitution of aniline it can be proved that the substituent first enters the amino-group, and then migrates to the ring: and it is quite probable that this happens in all cases.[2] It seems, in fact, to be a general rule that a substituent in the amino-group of aniline (as in $\phi{\cdot}NHX$) is capable of migrating to the ring, taking up mainly the para position, and to a less extent the ortho. Thus if aniline is treated with bleaching powder, the chloramine, $\phi{\cdot}NHCl$, is formed: this changes with the greatest ease into para- and a little ortho-chloraniline,

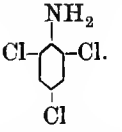


These can be converted by bleaching powder into chloramines, which go over

[1] Wieland, Gambarjan, *Ber.* **39.** 1499 (1906).

[2] Cf. Blanksma, *Rec. Trav.* **21.** 269 (*C.* **02.** ii. 513).

into o-p-dichloraniline; and this again gives a chloramine, which changes into symmetrical trichloraniline:



Finally, the chloramine prepared from this tri-chloro-compound, $C_6H_2Cl_3{\cdot}NHCl$, is quite a stable body. The chlorine cannot any longer migrate from the nitrogen to the nucleus, because the para and both the ortho positions are occupied, and it is not able to go into the meta.

The rate of change of acetyl-chloranilide into p-chlor-acetanilide,

$$\phi{\cdot}NCl{\cdot}CO{\cdot}CH_3 \longrightarrow Cl{\cdot}C_6H_4{\cdot}NH{\cdot}CO{\cdot}CH_3,$$

has been measured by Blanksma,[1] the amount of unchanged substance being determined by titration with potassium iodide and thiosulphate. The reaction is found to be monomolecular; it takes place more rapidly in acetic acid or in alcohol than in water; and it requires the presence of hydrochloric acid as a catalyst. The velocity constant is approximately proportional to the square of the concentration of the hydrochloric acid. The reaction is also catalysed by light.

This behaviour is not confined by any means to the halogens but is common to nearly all the N-substitution-products of aniline. It is worth while to collect the various instances in which it has been proved to occur, as otherwise the general nature of the reaction is liable to be overlooked.

Taking the typical form

$$C_6H_5{\cdot}N\langle{}^{H}_{X} \longrightarrow X{\cdot}C_6H_4{\cdot}NH_2,$$

X may belong to any of the following classes:—

1. Alkyl: as in the Hofmann reaction, e.g. methyl-aniline $\longrightarrow$ toluidine.
2. Chlorine or bromine, as in the above example.
3. Hydroxyl: thus β-phenyl-hydroxylamine gives p-amino-phenol:

$$C_6H_5N\langle{}^{OH}_{H} \longrightarrow HO{\cdot}C_6H_4{\cdot}NH_2.$$

4. NO. Thus methyl-phenyl-nitrosamine gives p-nitroso-methyl-aniline:

$$C_6H_5{-}N\langle{}^{NO}_{CH_3} \longrightarrow C_6H_4\langle{}^{NO}_{NHCH_3}$$

5. NO_2. Phenyl-nitramine, the so-called diazo-benzenic acid, $\phi{\cdot}NH{\cdot}NO_2$, gives a mixture of mainly para- with some ortho-nitraniline, $NO_2{\cdot}C_6H_4{\cdot}NH_2$.

6. SO_3H: as in $\phi{\cdot}NH{\cdot}SO_3H \longrightarrow HSO_3{\cdot}C_6H_4{\cdot}NH_2$ (o + p).

7. Acyl. This only occurs with the diacyl-compounds. But diacetanilide, $\phi{\cdot}N(CO{\cdot}CH_3)_2$, gives the isomeric acetyl-amino-benzophenone,

$$CH_3{\cdot}CO{\cdot}C_6H_4{\cdot}NH{\cdot}CO{\cdot}CH_3.$$

8. NH_2. Phenyl-hydrazine, $\phi NH{\cdot}NH\phi$, can be converted into para-phenylene-diamine, $H_2N{\cdot}C_6H_4{\cdot}NH_2$.

9. $-N{=}N{-}\phi$: as in the conversion of the diazo-amino-compounds into the amino-azo:

$$\phi{\cdot}NH{\cdot}N{=}N{\cdot}\phi \longrightarrow H_2N{\cdot}C_6H_4{\cdot}N{=}N{\cdot}\phi.$$

[1] *Rec. Trav.* **21.** 366; **22.** 290 (*C.* **03.** i. 141, ii. 241).

10. $-NH\phi$ and
11. $-C_6H_4NH_2$.

These two together form the most striking illustration: but it is often formulated in a way that conceals its real bearing. Hydrazobenzene, $\phi NH{\cdot}NH\phi$, a product of the alkaline reduction of nitrobenzene, is very readily acted on by acids, giving first a semidine, by the migration of the $-NH\phi$ to the para position on the other nucleus:— $H\bigcirc\!\!-NH-NH\phi \rightarrow \phi{\cdot}NH-\bigcirc\!\!-NH_2$.

The product is still a substituted aniline, and so a second change occurs, the substituent $C_6H_4NH_2$ migrating on to the nucleus, forming diamino-diphenyl or benzidine:— $H\bigcirc\!\!NH\bigcirc\!\!NH_2 \rightarrow H_2N\bigcirc\!\!-\bigcirc\!\!-NH_2$.

These cases will serve to show how very general the reaction is. It is remarkable that in nearly all of them a body of feebly basic or neutral or acidic character is converted into one of more pronounced basicity.

The property of giving on direct substitution ortho and para derivatives is common to all derivatives of benzene $C_6H_5{\cdot}X$ in which the compound HX cannot be directly oxidized to HOX. This is Crum Brown's rule. Since in the case of aniline we find that the substituent first enters the side chain and then passes on to the nucleus, we may ask whether the same is the case in all bodies belonging to this class. The most important substituents X of the ortho and para class are NH_2, OH, the hydrocarbon radicals, and the halogens. In the case of the halogens, this hypothesis is only possible if they assume a higher valency in the intermediate compound: and of this there is no evidence. In the case of the hydrocarbon radicals, though there is no intrinsic improbability of a reaction of this kind, there is also no evidence of its occurrence. With hydroxyl, on the other hand, there is direct evidence, though it is not so wide as with NH_2. Thus potassium phenyl sulphate is completely converted by heating in a sealed tube into potassium phenol-sulphonate:—

$$C_6H_5{\cdot}O{\cdot}SO_2OK \rightarrow KOSO_2{\cdot}C_6H_4{\cdot}OH:$$

and sodium phenyl carbonate if heated with soda to 200° gives sodium salicylate:— $C_6H_5{\cdot}O{\cdot}CO{\cdot}ONa \rightarrow NaO{\cdot}CO{\cdot}C_6H_4{\cdot}OH$.

Again, in the formation of oxyazo-compounds from diazo-derivatives and phenols, there is reason to think that a similar change takes place:—

$$\phi{\cdot}N_2{\cdot}OH + HO{\cdot}\phi \rightarrow \phi{\cdot}N_2{\cdot}O{\cdot}\phi \rightarrow \phi{\cdot}N_2-C_6H_4{\cdot}OH.$$

Whether similar intermediate compounds are formed in the case of other substitutions of phenol still remains to be proved.

In the direct substitution of aniline and similar bodies, it is often necessary to 'protect' the NH_2 group, as it is called, against secondary reactions. For example, aniline is very sensitive to oxidizing agents, and therefore, if it is treated with a halogen or with nitric acid, the molecule is liable to be completely broken up or to undergo complicated reactions, unless special precautions are taken. To avoid this, the amine group is protected commonly by acetylation. Thus, if aniline is to be nitrated, it is first converted into acetanilide, and then this is nitrated, and the nitro-acetanilide is then saponified by boiling with potash, whereby the acyl group is removed and nitraniline obtained. But

in many cases the presence of a strong acid is in itself a sufficient protection, forming the more stable aniline salt. This, however, is liable to affect the position of the substituent. For example, whereas acetanilide on nitration gives the ortho and ~~meta~~ para-nitro-products, as we should expect, and aniline itself does the same if nitrated with nitric acid alone at very low temperatures, if it is treated with nitric acid in presence of a very large excess of sulphuric acid, it gives mainly meta-nitraniline. In this case of course it is not aniline which is being nitrated, but aniline sulphate.

The influence of substituents on the basicity of aniline has been investigated by Farmer and Warth.[1] They determined the degree of hydrolysis of the hydrochlorides by shaking the aqueous solution with benzene, and observing the concentration of the base in the benzene layer. From this the concentration of the free base in the water can be calculated, and hence the hydrolysis. This does not give the real but the apparent dissociation-constant, as explained above: that is, it gives the value of the real $K \div (1 + b)$, where b is the (unknown) hydration-constant. It is, no doubt, owing to this complication that the results show a certain irregularity. The general conclusions are that the ortho position gives the greatest effect, and the meta the least; and as regards the nature of the substituents, the effect is in the order (strongly negative) NO_2, CO_2H, $N{=}N\phi$, Br, Cl, CH_3, CH_3O (weakly positive).

Halogen derivatives

Aniline, like phenol, can be chlorinated and brominated with great ease, by the action of chlorine or bromine on an aqueous solution of an aniline salt. Iodine can also substitute directly, since the excess of aniline removes the hydriodic acid formed. The halogens can also replace one another on the ring with singular ease: thus if para-bromaniline is chlorinated,[2] both trichloraniline and chlor-dibromaniline are formed, some of the bromine of the original compound being expelled by chlorine, and then attacking more of the compound.

It is remarkable that chlorine and bromine have very little action on aniline in strong sulphuric acid solution; and as far as they do react, produce meta-substitution-products.

In aqueous solution the final product of the action of the halogens is the symmetrical (di-ortho-para-)tri-halide. To get the lower products (mono- and di-haloid) it is best to treat acetanilide suspended in water with chlorine or bromine (or if iodine is to be introduced, to treat it with iodine monochloride). The first halogen atom goes mainly to the ortho position, the second mainly to the para. In this way by starting with aniline it is not possible to get beyond the tri-substitution-product: but by starting with meta-brom- or di-meta-brom-aniline the tetra- or penta-brom compound can be obtained, the three vacant places 2, 4, and 6 being filled up.

The diminution of basicity on introducing halogen atoms is shown by the fact that while the mono-halogen anilines still give salts stable to water,

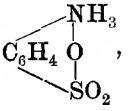
[1] *J. C. S.* **1904**. 1713. [2] Reed, Orton, *J. C. S.* **1907**. 1543.

the di-halogen compounds give salts which, if the acid is volatile, are largely decomposed on evaporating their aqueous solutions (i. e. which are highly hydrolysed): while the tri-halogen derivatives give no salts at all.

Sulphonic acids of aniline

Aniline is easily sulphonated by concentrated or slightly fuming sulphuric acid, giving first the para-mono-sulphonic acid, and then the ortho-para-disulphonic acid. The others may be got by indirect methods: for example the meta by reducing meta-nitrobenzene sulphonic acid. They may also be prepared by heating the haloid aryl-sulphonic acids with alcoholic ammonia to 160–180°, as the strongly negative sulphonic group (like the nitro-group) makes the halogen more mobile.

The mono-sulphonic acids of aniline are colourless bodies which crystallize well. Unlike the benzene sulphonic acids, which are excessively soluble in water, they only dissolve sparingly. Their melting-points are also much higher: thus while benzene sulphonic acid melts at 50°, aniline para-sulphonic acid blackens without melting at 280–300°. They form salts with bases but not with acids, and hence dissolve in aqueous alkalies and are reprecipitated by acids. All these peculiarities indicate that they are intramolecular salts, e. g.



as in the parallel case of the amino-acids. This is confirmed by the fact that they cannot be acetylated, while their sodium salts, which must have a free NH_2 group, can.

Nitranilines

Aniline can be nitrated directly if it is dissolved in concentrated sulphuric acid, cooled to 0°, and the calculated quantity of nitric acid dissolved in a great excess of sulphuric acid slowly added. These precautions are necessary in order to prevent the oxidation of the aniline. The product is a mixture of meta and para-nitraniline with a little ortho. Alkyl and acyl anilines behave in the same way.[1]

The nitranilines may also be got by the partial reduction of the poly-nitro-compounds, as in the preparation of meta-nitraniline from meta-dinitro-benzene with ammonium sulphide.

The great effect of the nitro-group in weakening the basicity of the NH_2 and its dependence on position were shown by Lellmann[2] by a rough but ingenious method. He took an equal weight (0·5171 gr.) of the hydrochlorides of each of the three nitranilines, boiled it up with 27 c.c. of water, and evaporated the solution to dryness at 75°. The loss of hydrochloric acid gives an approximate measure of the degree of hydrolysis. He found that of the ortho-nitraniline salt, 63·8 per cent. was decomposed under these

[1] Tingle, Blanck, *Am. Ch. J.* **36**. 605 (*C.* **07**. i. 632).

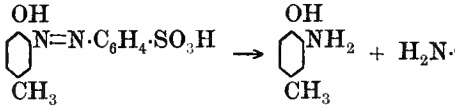
[2] *Ber.* **17**. 2719 (1884).

conditions, of the meta 3·4, and of the para 13·1. A more exact determination[1] of the strength of these bases, by the increase of solubility of slightly soluble acids (cinnamic and p-nitro-benzoic), shows their dissociation constants to be

ortho $0{\cdot}01 \times 10^{-12}$
meta $4{\cdot}0 \times 10^{-12}$
para $1{\cdot}0 \times 10^{-12}$.

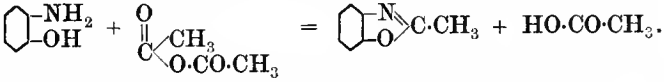
Hydroxy-anilines, or aminophenols

They are obtained by the reduction of the nitrophenols and of the azophenols or oxy-azo-compounds. The latter are often used for preparing the more complicated derivatives, as they are easy to make by coupling the phenols with the diazo-compounds. Thus if sulphanilic acid is diazotized and coupled with, say, para-cresol, an oxy-azo body is formed which on reduction breaks up, as usual, between the two nitrogen atoms, giving amino-cresol:—



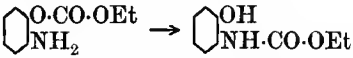
They are also formed by intramolecular rearrangement from the β-phenylhydroxylamines: $C_6H_5NHOH \longrightarrow HO{\cdot}C_6H_4{\cdot}NH_2$. Hence they are often produced in reactions which would be expected to lead to the hydroxylamines, as in the electrolytic reduction of the aromatic nitro-compounds.

Their properties are both basic and acidic. They form stable salts with acids, and also dissolve in aqueous alkalies. The ortho-compounds condense very readily to form a second (nitrogenous) ring, giving, for example, with acid anhydrides the so-called anhydro-bases, or benzoxazoles:—



The para-aminophenols, on the other hand, are readily oxidized to quinones. These two reactions are characteristic of the two classes of ortho and para di-derivatives of benzene respectively.

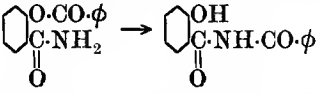
The oxygen esters of the ortho-aminophenols undergo a remarkable intramolecular change,[2] the acyl group migrating from the oxygen to the nitrogen, with the formation of a urethane: for example:—



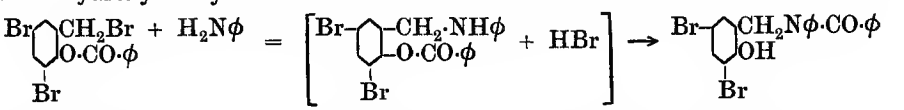
The change takes place in acid solution, and its velocity can be measured by means of the conductivity.[3] The salt is partly hydrolysed in solution into free base and acid, and it is found that it is only the free base (the hydrolysed part) which changes, and that for this part the reaction is monomolecular. Einhorn and Pfyl[4] have shown that it is only the ortho-aminophenol derivatives which undergo this change, and not the meta or para.

[1] Löwenherz, *Z. Ph. Ch.* **25**. 385 (1898). [2] Ransom, *Ber.* **33**. 199 (1900).
[3] Stieglitz, Upson, *Am. Ch. J.* **31**. 458 (*C.* **04**. ii. 94). [4] *Ann.* **311**. 34 (1900).

That is, the acyl group will not travel further than to an NH_2 attached to the next carbon on the ring. But if the NH_2 is on a side chain, the acyl will go further. Thus[1] a benzoyl group will go from the oxygen to the nitrogen of salicylamide (i. e. to a nitrogen attached to the next carbon atom but two):—



and Auwers[2] finds a similar migration to the nitrogen of a substituted ortho-hydroxy-benzylamine:—



The intermediate compound in this case has not been isolated, but there can be no doubt that it is formed. The reaction takes place more easily the more negative the acyl group and the more basic the nitrogen.

These facts indicate that the nitrogen attached to the carbon of the side chain is nearer for the purposes of reaction than that on the meta carbon atom of the ring. (Compare the fact that meta-(iso)-phthalic acid will not give an anhydride though the corresponding open-chain acid, glutaric acid, does so readily.) The reactivity of the side-chain compound is certainly not due to any peculiarity of the open-chain compounds as such: for no such migration of acyl groups occurs with the purely fatty derivatives, the O-acyl esters of the amino-alcohols, for example $\begin{matrix}CH_2\cdot NH_2\\ CH_2\cdot O\cdot CO\cdot\phi\end{matrix}$, being perfectly stable. Nor does it occur even with the aromatic side-chain derivatives, if the amino-group is on the nucleus and the hydroxyl on the side chain, as in  whose O-acyl ester is also quite stable.

Homologues of aniline

The homologues of aniline (with the alkyl groups attached to the nucleus) can be made by reducing the nitro-derivatives of the homologues of benzene, in cases where these last can be easily obtained, and will give the required nitro-derivatives. Or the corresponding phenols may be heated with the compound of zinc or calcium chloride and ammonia.

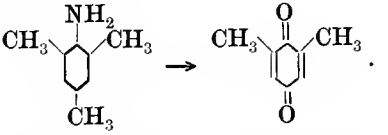
Another method is to introduce the alkyls first into the amino-group of aniline, and then transfer them to the nucleus by means of the Hofmann reaction (heating the hydrochlorides to 250–350°). The alkyls can only be put into the ortho and para positions in this way: but by starting with symmetrical meta-xylidine (1 : 3 : 5), where the two meta positions are already occupied, Hofmann prepared amino-pentamethyl-benzene.

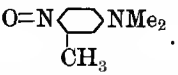
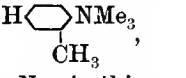
Their behaviour is in general that of aniline, except in so far as the side chains interfere: thus para-acettoluidide on nitration gives not the para but the ortho nitro-compound.

[1] McConnan, Titherley, *J. C. S.* **1906**. 1318.

[2] *Ann.* **332**. 159 (1904); **364**. 147 (1909).

Like aniline itself they tend to form quinones on oxidation; and this tendency is so strong that if there is a methyl group in the para position to the NH_2, it is often eliminated. For example, mesidine is very easily converted into meta-xyloquinone:—



In some cases the side chains have unexpected effects, as is shown in the formation of nitroso-derivatives from the tertiary amines. Dimethyl-aniline of course gives the para-nitroso-compound, $O{=}N\langle\rangle NMe_2$. Dimethyl-para-toluidine, $CH_3\langle\rangle NMe_2$, gives no nitroso-derivative at all. This is to be expected, since the para position is occupied. Dimethyl-meta-toluidine, where the para position is free, behaves like aniline, and gives a para-nitroso-compound,  . But dimethyl-ortho-toluidine,  , though it has the para position open, gives no nitroso-derivative. Nor is this the only reaction in which dimethyl-ortho-toluidine shows that for some unknown reason the para hydrogen is unusually firmly attached to the nucleus. It refuses to give it up either to couple with diazo-compounds or to condense with aldehydes: reactions which occur with dimethyl-aniline itself with the greatest ease.

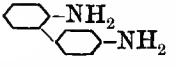
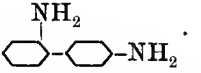
The oxidation of the amines leads to a variety of products, and has been investigated in great detail; but it will be more convenient to deal with it later,[1] in connexion with the analogous question of the reduction of the nitro-compounds.

BENZIDINE DERIVATIVES

The diamines of diphenyl are of interest from the peculiar reaction in which they are produced by intramolecular change from the hydrazo-compounds:

$H\text{-}\langle\rangle\text{-}NH\text{-}NH\langle\rangle\text{-}H \rightarrow H\text{-}\langle\rangle\text{-}NH\langle\rangle\text{-}NH_2 \rightarrow H_2N\langle\rangle\text{-}\langle\rangle\text{-}NH_2$,

amino-diphenylamine or semidine being first formed. As usual, it is normally the para position that is occupied, di-para-diamino-diphenyl or benzidine being produced. But it is not necessary that the final product should be a benzidine. The reaction may stop at the first stage, giving a semidine, or the second stage may take place, but in a different way, the substituent ($C_6H_4{\cdot}NH_2$) migrating not to the para but to the ortho position,

 or as it is usually written  .

This ortho-derivative is known as diphenyline. Which of the three possible derivatives is formed depends on the substituents present in the two nuclei:

[1] See p. 162.

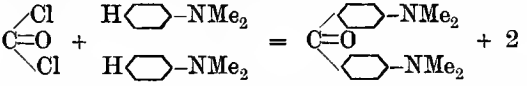
in the case of hydrazo-benzene itself the products are mainly benzidine, a little diphenyline, and no semidine.

Many of the salts are remarkable for their insolubility in water, and this has been made use of for the quantitative determination of certain acids, such as sulphuric and tungstic.[1]

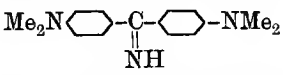
AMINO-DI- AND TRI-PHENYL-METHANES

Some of the amino-derivatives of di- and tri-phenyl-methane are of great practical importance as dyes; and they are also of theoretical interest in respect both of their mode of preparation and of their structure.

The only important class of diphenyl-methane dyes is the auramines. They are obtained from a body which is also a valuable source of the triphenyl-methane dyes, tetramethyl-diamino-benzophenone, known as Michler's ketone. This body is prepared by saturating dimethyl-aniline with phosgene gas:—



This ketone is extraordinarily reactive, as is also the benzhydrol (secondary alcohol) $HC(OH)(C_6H_4{\cdot}NMe_2)_2$ obtained from it by reduction. The ketone condenses with ammonia to give an imine

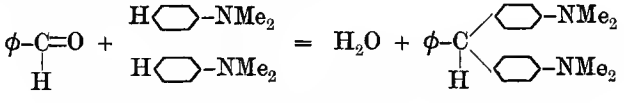


whose hydrochloric acid salt is auramine, the purest yellow dye known.

Of more importance are the triphenyl-methane dyes, which include the earliest aniline dyes made on the commercial scale. In 1843 Hofmann observed that the so-called aniline oil could be converted by oxidation into coloured substances. The first dye to be put on the market was W. H. Perkin's 'Mauve' in 1857: this was an alcoholic solution of the product of treating aniline sulphate with potassium chromate. In 1859 fuchsin was made in France, by oxidizing aniline oil with stannic chloride.

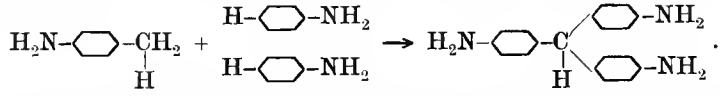
The processes by which the triphenyl-methane dyes are made are very various. They are formed in many quite unexpected reactions, in which aniline or an alkyl aniline is oxidized in presence of some compound which can supply the linking methane carbon atom. So great is the tendency to form compounds of this type, that even if dimethyl-aniline is oxidized alone, one methyl group is split off, as has already been mentioned, to give the necessary link.

They can also be made by starting with benzaldehyde, whose CHO group supplies the methane carbon. If this is heated with dimethyl-aniline, it condenses with it with loss of water, giving tetramethyl-diamino-triphenyl-methane, the leuco-base of malachite green:—

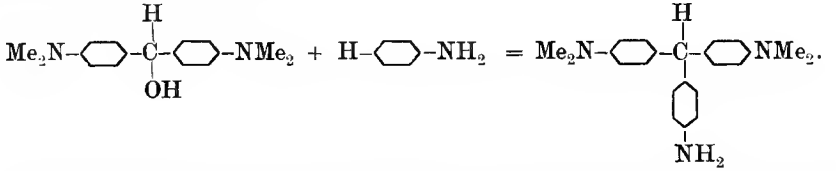


[1] Friedheim, Nydegger, *C.* **07.** i. 504; v. Knorre, ib. 993.

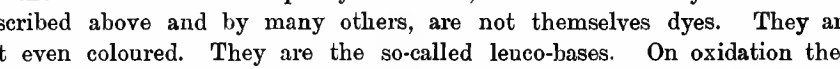
or a mixture of para-toluidine and aniline may be oxidized, which gives para-leucaniline.



Or they can be prepared from Michler's ketone, or better from its reduction-product the benzhydrol. This condenses with aniline to give tetramethyl-triamino-triphenyl-methane:—



These bodies also appear to exchange their nuclei with remarkable ease, considering that this implies the breakage of the link between carbon and carbon. Thus[1] para-diamino-triphenyl-methane, if it is heated with a large excess of ortho-toluidine and its hydrochloride, goes over into diamino-ditolyl-phenyl-methane, which when heated with excess of aniline and its hydrochloride goes back to the triphenyl-methane derivative:—



The di- and tri-amino-triphenyl-methanes, which are made by the methods described above and by many others, are not themselves dyes. They are not even coloured. They are the so-called leuco-bases. On oxidation they readily give compounds whose composition is that of the leuco-bases plus one atom of oxygen. These bodies have the hydrogen on the methane carbon replaced by hydroxyl: they are carbinols or tertiary alcohols, e. g. $(Me_2N\langle\rangle-)_3\cdot COH$. These again are not dyes, but they form salts with acids which are. The colour of the dyes so formed depends on their constitution, and can be altered at will within certain rather wide limits by the successive introduction of various groups. The main facts with regard to the changes of colour so produced are as follows:—

The amino-triphenyl-methanes do not yield dyes at all on oxidation (though they may give coloured substances) unless they contain at least two amino-groups in the para position. Di-para-diamino-triphenyl-carbinol is a violet dye, which, however, is not sufficiently fast to be used commercially. The tri-para-triamino-compound is para-leucaniline; on oxidation it gives para-rosaniline, the carbinol, whose hydrochloric acid salt is para-fuchsin, a valuable red dye.

The introduction of substituents such as NO_2 into the nucleus has a distinct though not a very great effect on the colour. Noelting and Gerlinger[2] have examined the influence on the colour of malachite green (the salt of

[1] Vongerichten, Weilinger, *C.* **04.** ii. 226.

[2] *Ber.* **39.** 2041 (1906). Cf. Reitzenstein, Runge, *J. pr. Ch.* [2] **71.** 57; Reitzenstein, Rothschild, **73.** 192; Reitzenstein, Schwerdt, **75.** 369 (*C.* **05.** i. 1020; **06.** i. 1168; **07.** ii. 1412); Bielecki, Koloniew, *C.* **08.** ii. 876; Finger, *J. pr. Ch.* [2] **79.** 492 (*C.* **09.** ii. 362).

tetramethyl-diamino-triphenyl-carbinol $(Me_2N{\cdot}C_6H_4{\cdot})_2C(OH)C_6H_5$ of substituents introduced into the nucleus which does not contain an amino-group. They find that if these are in the ortho position the colour is changed towards blue, and if in the para, towards yellow: in the meta, little effect is produced. Of the substituents examined, chlorine had the greatest effect, then NO_2, then methyl, and least of all methoxyl, CH_3O, which was very feeble.

The introduction of hydrocarbon radicals into the amino-groups, which is easier, and therefore of greater commercial value, has more influence on the colour. The simple diamino-compounds (all substituents are para unless otherwise stated) are red or violet, but on alkylation they give valuable green dyes. The red fuchsin (triamino-) becomes increasingly violet as successive alkyl groups are introduced: while the introduction of phenyl groups causes the colour to pass over into blue.

But it is remarkable that if an acid radical such as acetyl is introduced into an amino-group, or if it is converted into a quaternary salt by the addition of alkyl halide, its influence on the colour is entirely destroyed. Thus hexa-methyl-para-fuchsin, whose leuco-base is $(Me_2N{\cdot}C_6H_4{\cdot})_3CH$, is crystal violet, an important dye. On combination with methyl iodide the leuco-base gives $(Me_2N{\cdot}C_6H_4{\cdot})_2CH{\cdot}C_6H_4{\cdot}[NMe_3I]$, and this body on oxidation gives a green dye, that is, a dye which has the same colour as it would have if the group in brackets were replaced by hydrogen, which would give malachite green.

Constitution of the rosaniline dyes

This includes two distinct questions, firstly the constitution of the leuco-bases, which has been satisfactorily made out, and secondly that of the salts of their oxidation-products, the true dyes, which is more open to dispute.

The nomenclature of the bodies is rather confusing. There are two groups of rosaniline compounds, one with 19 and the other with 20 carbon atoms in the molecule. In each we have to distinguish the leuco-base, its oxidation product (the carbinol), and the salt (usually the hydrochloride) of the latter, which is the true dye. The names are:—

	C_{19}	C_{20}
Leuco-base	Para-leucaniline	Leucaniline
Carbinol	Para-rosaniline	Rosaniline
Salt (dye)	Para-fuchsin	Fuchsin

The first question is the constitution of the leuco-bases. Rosaniline was isolated and analysed by Hofmann in 1862–3, but our knowledge of its constitution is due to the work of Emil and Otto Fischer in 1876–8. Rosaniline had been shown to contain three amino-groups, because it gave a compound with nitrous acid which on warming lost all its nitrogen to form a body with three hydroxyl groups. Leucaniline gave a diazo-compound which when treated with absolute alcohol was converted into an unknown hydrocarbon $C_{20}H_{18}$.

E. and O. Fischer repeated this experiment with para-leucaniline, the next lower homologue of leucaniline, containing one CH_2 less. This gave the hydrocarbon $C_{19}H_{16}$, which they found to be identical with triphenyl-methane.

Thus the key to the solution of the problem was discovered: the compounds were shown to be triphenyl-methane derivatives, and para-leucaniline to be triamino-triphenyl-methane. It remained only to find the position of the amino-groups.

Now benzaldehyde condenses with aniline to give a diamino-triphenyl-methane:— $\phi\cdot CHO + 2\,C_6H_5\cdot NH_2 = \phi\cdot CH(C_6H_4NH_2)_2 + H_2O.$

If this is diazotized the two amino-groups are replaced by hydroxyl, giving dioxy-triphenyl-methane: and when this is melted with potash it splits off the phenyl group to form dioxy-benzophenone, $CO(C_6H_4\cdot OH)_2$. This compound was proved to have the two hydroxyls in the para position by the following synthesis.

Benzaldehyde condenses in presence of potassium cyanide to benzoin, which on oxidation yields benzil; this when boiled with potash undergoes a remarkable rearrangement and forms benzilic acid, which on oxidation loses CO_2 and forms benzophenone:—

$$\phi\cdot CHO + CHO\cdot\phi \rightarrow \underset{\text{Benzoin}}{\phi\cdot CHOH\cdot CO\cdot\phi} \rightarrow \underset{\text{Benzil}}{\phi\cdot CO\cdot CO\cdot\phi}$$

$$\rightarrow \underset{\underset{\text{Benzilic acid}}{\phi\cdot C(OH)\phi}}{\overset{|}{\underset{COOH}{}}} \rightarrow \underset{\text{Benzophenone}}{\phi\cdot CO\cdot\phi.}$$

Starting with anisaldehyde (para-methoxy-benzaldehyde) a precisely similar series of reactions can be performed:—

$$CH_3O\langle\rangle CHO + CHO\langle\rangle OCH_3 \rightarrow \underset{\text{Anisoin}}{CH_3O\langle\rangle CHOH\cdot CO\langle\rangle OCH_3}$$

$$\rightarrow \underset{\text{Anisil}}{CH_3O\langle\rangle COCO\langle\rangle OCH_3} \rightarrow \underset{\underset{\text{Anisilic acid}}{\overset{|}{\underset{COOH}{}}}}{CH_3O\langle\rangle C(OH)\text{–}\langle\rangle OCH_3}$$

$$\rightarrow CH_3O\langle\rangle CO\langle\rangle OCH_3,$$

giving ultimately the dimethyl-ether of para-dioxy-benzophenone. This ether is found to yield and to be formed from the same dioxy-benzophenone as that got from the diamino-triphenyl-methane. Hence this diamino-compound, the condensation-product of aniline and benzaldehyde, must have the two amino-groups in the para position.

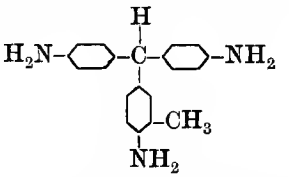
Now para-nitro-benzaldehyde condenses with aniline in the same way as benzaldehyde itself. The product must have the two amino-groups on two of the nuclei in the para position, and also the nitro-group in the para position on the third, thus:—

$$NH_2\langle\rangle CH\langle\rangle NH_2$$
$$\langle\rangle$$
$$NO_2$$

When this compound has the nitro-group reduced to NH_2, it gives para-leucaniline, which thus is proved to have all the three amino-groups in the para position, and to be tri-para-triamino-tri-phenyl-methane.

Finally, if para-nitro-meta-toluic aldehyde is condensed with aniline and

the product reduced, leucaniline is formed, which therefore has the formula:—



Thus the formulae of the leuco-bases are determined. Those of the dye-bases (carbinols) are derived from them by substituting hydroxyl for the hydrogen attached to the methane carbon.

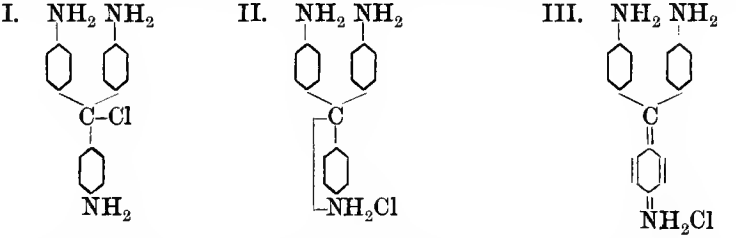
We now come to the much more difficult problem of the constitution of the salts of the carbinols, which are the real dyes, para-fuchsin and fuchsin. Take the case of the simplest of these bodies, para-fuchsin. Para-leucaniline is proved to be tri-para-triamino-triphenyl-methane. When this is oxidized it gives the corresponding carbinol, which is certainly $HO{\cdot}C(C_6H_4{\cdot}NH_2)_3$: this is para-rosaniline. On treatment with hydrochloric acid it forms the dye para-fuchsin. Analysis shows that one molecule of the carbinol reacts with one molecule of acid, and one molecule of water is eliminated. The resulting compound may be formulated in three ways.

1. The hydroxyl of the carbinol may be directly replaced by chlorine. This would give a haloid ester, in the same way that alcohol gives ethyl chloride. This is Rosenstiehl's formula.

2. The hydrochloric acid may add on to one amino-group, and the NH_3Cl so produced may split off water with the COH, the nitrogen becoming linked with the methane carbon. (O. and E. Fischer.)

3. The addition of acid and loss of water may occur in the same way as in the last case, but instead of the nitrogen becoming linked to the methane carbon, the ring may become quinoid, and be doubly linked on the one side to the methane carbon and on the other to the dyad group $=NH_2Cl$. (Nietzki.)

I. II. III.



Rosenstiehl O. and E. Fischer Nietzki

Formulae 2 and 3 differ in the same way as do the old and the new formulae for quinone (the peroxide and the diktoene): and as the former has been abandoned in favour of the latter in the case of quinone, we may provisionally leave the corresponding formula (2) out of consideration, although, as will be seen later, there is some reason to think that these dyes may not be strictly analogous to the simple quinones. The real question is between Rosenstiehl's and Nietzki's formulae. Rosenstiehl's theory, representing the salt as an ester, gives a peculiarly simple explanation of its formation from aniline and carbon tetrachloride $3\ \phi NH_2 + CCl_4 = (NH_2C_6H_4)_3CCl + 3\ HCl$.

But the balance of evidence is strongly in favour of Nietzki's view. For example, if para-fuchsin is warmed with potassium cyanide and alcohol, it gives rosaniline hydrocyanide, which is certainly a nitrile, having the CN attached to carbon thus $(NH_2C_6H_4)_3C{\cdot}CN$. This at first sight appears in favour of Rosenstiehl's view, which represents it as a simple replacement of chlorine by cyanogen. But if so, the product ought to be similar in properties to the fuchsin, which it is not. The cyanide is colourless, gives colourless salts (of the NH_2 groups) with acids, and does not decompose, as fuchsin does, with bases into the carbinol and an alkaline salt. Hence it is clear that the two compounds are not analogous in structure, and that in para-fuchsin the chlorine is not on the methane carbon.

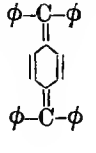
It has been urged in favour of Rosenstiehl's formula that para-fuchsin can take up three more molecules of hydrochloric acid to give a compound the composition of which is that of the carbinol + 4 HCl − H_2O: and that therefore the three nitrogen atoms must be trivalent, and that one cannot already have formed a salt. But this reaction is really one of the strongest arguments on the other side. For in the first place the acid salt so produced is colourless (or practically so) and hence cannot retain the structure of the original dye. In the second place it is not formed instantaneously but slowly. Now if its formation consisted merely in the addition of hydrochloric acid to an amino-group, this should occur at once: for there is no known case where the addition of acid to a tertiary nitrogen atom is slow: and also the product should be similar to the original dye. But if Nietzki's formula is accepted, we should expect the formation of this acid salt to be slow, and to be accompanied by a loss of colour. For on this formula the dye-salt can take up two molecules of hydrochloric acid at once:—

$$(H_2NC_6H_4)_2{=}C{=}C_6H_4{=}NH_2Cl \longrightarrow (ClH_3NC_6H_4)_2{=}C{=}C_6H_4NH_2Cl$$

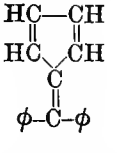
but the third acid molecule can only be taken up by destroying the quinoid grouping, e.g. to form $(ClH_3NC_6H_4)_2{=}C\langle^{C_6H_4NH_3Cl}_{Cl}$, which must take time, as does the formation of the quinoid itself, and must destroy the colour, as it destroys the quinoid structure.

Further, there is no reason on Rosenstiehl's hypothesis why the bodies should be coloured at all. The carbinol and the cyanide, whose structure is strictly analogous to that which he attributes to the dye, are colourless. But the quinoid ring is constantly found to be accompanied by colour, both in the quinones themselves, and in at least the majority of their derivatives. The tendency of bodies of this type to be coloured is well illustrated by two hydrocarbons discovered by Thiele, which have a close analogy to Nietzki's fuchsin formula (III), as far as the carbon skeleton is concerned, and about whose structure there can be no doubt.[1] They are tetraphenyl-para-xylylene (I) and diphenyl-fulvene (II).

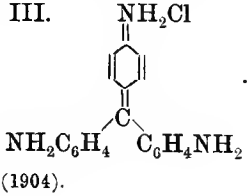
I.



II.



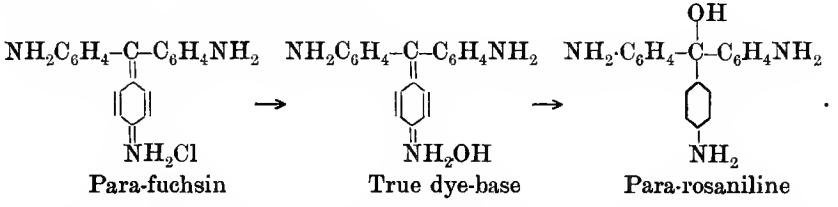
III.



[1] *Ber.* **33.** 666 (1900); **37.** 1465 (1904).

The two hydrocarbons are brilliantly coloured. The first crystallizes in needles of the colour of powdered potassium bichromate, and gives deep yellow or orange solutions. The fulvene derivative forms deep red prisms. The analogy between these three compounds shows that we have good reason to expect a body with Nietzki's formula to be coloured. Diphenyl-fulvene is also of interest as bearing on the question of the formula of quinone and its derivatives. The supporters of the older peroxide formula held that in quinone the nucleus retained its aromatic structure, whereas on the diketone theory it is supposed that this structure is destroyed, and replaced by an arrangement of ordinary double bonds. Now in diphenyl-fulvene there is just such an arrangement of double bonds: and a peroxide-like linking, much more an aromatic structure, is inconceivable: and yet the characteristic brilliant colour remains. This question, which is still very obscure, will be further discussed in dealing with the nitrophenols.

But the most conclusive evidence for Nietzki's theory is derived from the physico-chemical investigation of the change of the coloured rosaniline derivatives into the colourless. Hantzsch[1] has shown that the fuchsins and the triphenyl-methane dyes in general are electrolytically dissociated in water to a high degree. This in itself is evidence that they are true salts of pentavalent nitrogen and not esters. Again, we know that when para-fuchsin is treated with alkali it is converted into the carbinol, para-rosaniline. On Rosenstiehl's formula this is only the replacement of the chlorine by hydroxyl. But on the quinoid formula it must occur in two stages, a quaternary hydroxide, the true dye-base, being formed first:—

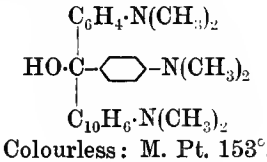


Hantzsch has shown that these intermediate compounds really exist. If a dilute (red) solution of para-fuchsin is treated with an equivalent of soda, the electric conductivity is at first very nearly the sum of those of the two solutions separately. Since the solution must contain the ions of sodium chloride, it follows that it must also contain the ions of a highly dissociated ammonium hydroxide. At the same time the solution is still coloured. But on standing, and more rapidly the higher the temperature, the conductivity diminishes, and with it the colour: till finally, after some hours at low temperatures, you get a colourless solution, whose conductivity is that of the sodium chloride it contains. This can only be explained in one way. The first product of the action of the soda on the para-fuchsin must be the formation of a highly dissociated coloured hydroxide, which then changes on standing into the colourless non-dissociated carbinol. Hence the fuchsin is not the chloride of the carbinol, but of an isomeric basic hydroxide, the true dye-base

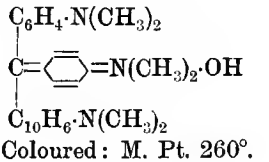
[1] Hantzsch, Osswald, *Ber.* **33**. 278 (1900).

required by Nietzki's formula. The carbinol belongs to the class of bodies, recently found to be of considerable extent, known as pseudobases: which are not themselves basic, but in the presence of an acid are converted into the salts of an isomeric (tautomeric) base.

Recently a case has been discovered[1] in which two forms can actually be isolated. Hexamethyl-triamino-diphenyl-naphthyl-carbinol when precipitated from the salt by alkali and recrystallized from xylene forms dark green crystals melting at 260°, which yield red or red-violet solutions, and give the bright blue colour of the dye with dilute acids at once. If the body is recrystallized several times from ether it is converted into a colourless substance melting at 153°, which forms colourless solutions, and only gives the blue colour with acids on warming. The two have the same composition, and it is obvious that the colourless body is the carbinol. If, as Noelting and Philipp assume, the other isomer is the dye-base, we may write the formulae of the two:—



Colourless: M. Pt. 153°.
Carbinol.



Coloured: M. Pt. 260°.
Dye-base.

But as Willstätter[2] has pointed out, the high-melting isomer has a different colour from the dye, and therefore must have a different constitution. What this may be, we are scarcely yet in a position to consider: but the body is evidently more closely related to the dye than is the carbinol, since it is converted into it more easily.

In Hantzsch's work, the carbinol gradually separated out during the experiment: and it might be objected that this separation was the cause of the diminution of conductivity and colour. But similar results are obtained by using solutions so dilute that the carbinol remains in solution, so that this objection falls to the ground. By observing the conductivity at definite intervals of time it is possible to measure the rate at which the dye-base goes over into the carbinol. From the results of Hantzsch and Osswald Gerlinger[3] showed that the reaction was bimolecular; that is, the rate of change was proportional to the square of the concentration of the dye-base. By using the colour as a measure of the amount of dye-base present, it has been shown[4] that in the presence of a large excess of alkali (whose concentration may be taken as constant during an experiment) the reaction is monomolecular, and the constant proportional to the amount of alkali. Hence it follows that the rate of production of carbinol is proportional to the product of the concentrations of the cation of the base and of the hydroxyl. Hence if the hydroxyl remains constant, the reaction is monomolecular: if the two vary together, as in Hantzsch's experiments, it is bimolecular. This seems to be the general rule: that where a dissociated substance changes tautomerically into an un-

[1] Noelting, Philipp, *Ber.* **41.** 579 (1908). [2] *Ber.* **41.** 1459 (1908). [3] *Ber.* **37.** 3958 (1904).
[4] Sidgwick, Moore, *Z. Ph. Ch.* **58.** 385 (1907); *J. C. S.* **1909.** 889; Sidgwick, Rivett, ib. 899.

dissociated, the velocity is proportional to the product of the concentrations of the two ions. It has been observed by Walker and Hambly[1] for the change of ammonium cyanate into urea, and by Dimroth[2] for a similar change in certain triazole derivatives. It is natural to conclude that in such cases the ions combine directly to the undissociated tautomer; and that in the case of these dyes, for example, it is the ions and not the undissociated dye-base that go over into the carbinol. But this conclusion is not certain. The results are equally compatible[3] with its being the undissociated base and that alone which undergoes the change. For however strong the base is there must be some of it undissociated: and the concentration of this part will by the law of mass-action be proportional to the product of the concentrations of the two ions. If, therefore, it is only the undissociated base that reacts, the rate of change will be proportional to its concentration, and so also to that of the ions: which is precisely what is found. The results are therefore equally compatible with either view, and at present it does not seem possible to decide definitely between them.

The rosaniline dyes seem to have a certain tendency to go back from the coloured quinoid form to the colourless non-quinoid form at very low temperatures: for it has been shown[4] that the alcoholic solutions of the rosaniline dyes (including crystal violet, but not malachite green), if they are cooled with liquid air, become nearly colourless. If an aqueous solution is treated with sulphur dioxide, it loses its colour, owing to the formation of an acid sulphite[5]; but if an aldehyde is added, this removes the sulphurous acid, and the colour is restored. This is Schiff's test for aldehydes.

Nietzki's theory as to the constitution of these dyes is entirely confirmed by the behaviour of their salts, as has already been mentioned. Of these salts various and somewhat conflicting accounts have been given, but the main facts are as follows.[6] The compounds all give at least three series of salts, though they cannot in all cases be isolated. (1) The carbinol combines in the cold with as many molecules of a monobasic acid as there are nitrogen atoms in the molecule, to form a colourless salt. This is obviously (to take for simplicity the case of a diamino-body) $\phi\cdot COH(C_6H_4\cdot NH_2\cdot HX)_2$. In solution this gradually changes with loss of water (and probably also of one of its acid molecules) into the dye itself (2), for example $H_2N\cdot C_6H_4\cdot C\phi{=}C_6H_4{=}NH_2X$. In presence of excess of acid this takes up at once another molecule of acid, without change of colour in the solution, forming (3) $XNH_3\cdot C_6H_4\cdot C\phi{=}C_6H_4{=}NH_2X$, and then slowly a third molecule, by the destruction of the quinoid grouping

$$\begin{matrix}\phi\\|\\C\\|\\X\end{matrix}$$

and hence also of the colour, giving (4) $XNH_3\cdot C_6H_4\cdot C(\phi)(X)\cdot C_6H_4\cdot NH_3X$. Of these salts all except (3) have been isolated. The last (4) is orange in the solid state, but its colour is infinitesimal in comparison with that of the dye.

[1] *J. C. S.* **1895**. 746. [2] *Ann.* **335**. i. (1904).
[3] Goldschmidt, *Z. f. Elektrochem.* **11**. 5 (*C.* **05**. i. 451).
[4] Schmidlin, *C. R.* **139**. 731 (*C.* **05**. i. 96). [5] Dürrschnabel, Weil, *Ber.* **38**. 3492 (1905).
[6] Lamprecht, Weil, *Ber.* **37**. 3058 (1904); **38**. 270 (1905); Hantzsch, *Ber.* **33**. 753 (1900).

If a solution of fuchsin is treated with alkali and at once extracted with ether, a brown substance dissolves in the ether which is a quinone imine, $(NH_2 \cdot C_6H_4)_2C{=}C_6H_4{=}NH$, known from its discoverer as the Homolka base. Baeyer and Villiger[1] have urged that this is the only immediate product of the action of alkali on the dye, and that it takes up water to form the carbinol, without any true ammonium base being formed at all. But this would not explain[2] the high conductivity of the freshly prepared solution, nor the fact that the completely alkylated dyes (such as malachite green and crystal violet) behave in precisely the same way, though they cannot possibly form an imine. The imine is no doubt formed in the aqueous solution to a small extent by the loss of water from the true dye-base, and being much more soluble in ether is removed by it, and then the disturbed equilibrium restored by the production of more imine, which is again removed, and so on: just as ammonia can be removed from its aqueous solution, for example by a stream of air, in the anhydrous form of NH_3.

DIAMINES

Some of these bodies have already been mentioned, for example the diamino-acids among the products of the hydrolysis of proteins: and the triphenyl-methane dyes are of course di- and tri-amino-compounds. But the important reactions of all these bodies are closely analogous to those of the simple mon-amino-compounds, and therefore they have been discussed along with the latter.

The aliphatic diamines differ very greatly from the aromatic, since in addition to the differences already pointed out between the alkyl- and arylamines the interaction of the two amino-groups (always an important class of reactions of di-substitution-products) is much affected by the greater rigidity which results when the intervening carbon atoms form part of a benzene ring.

Aliphatic diamines

Methods of preparation.

1. From the di-halogen-derivatives of the hydrocarbons which have the halogens on different carbon atoms, by treatment with ammonia, generally by heating in sealed tubes with alcoholic ammonia to 100°:—

$$\begin{matrix} CH_2Br \\ | \\ CH_2Br \end{matrix} + \begin{matrix} NH_3 \\ NH_3 \end{matrix} = \begin{matrix} CH_2 \cdot NH_2 \\ | \\ CH_2 \cdot NH_2 \end{matrix} + 2\ HBr.$$

In this reaction secondary and tertiary derivatives are formed at the same time, either with open chains as $NH_2 \cdot CH_2 \cdot CH_2 \cdot NH \cdot CH_2 \cdot CH_2 \cdot NH_2$, or with closed chains, as $NH\begin{matrix} CH_2 \cdot CH_2 \\ CH_2 \cdot CH_2 \end{matrix}\!\!>\!NH$, and the separation of these products is difficult.

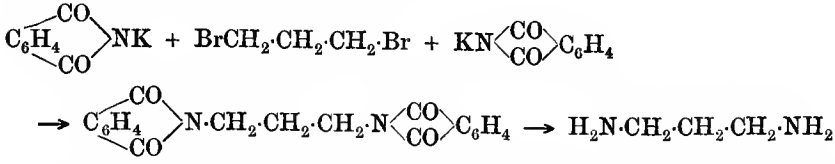
2. By the reduction with sodium in alcoholic solution of the nitriles of the dibasic acids, such as succinonitrile,

$$\begin{matrix} CH_2 \cdot C{\equiv}N \\ | \\ CH_2 \cdot C{\equiv}N \end{matrix} + 4\ H_2 = \begin{matrix} CH_2 \cdot CH_2 \cdot NH_2 \\ | \\ CH_2 \cdot CH_2 \cdot NH_2 \end{matrix}.$$

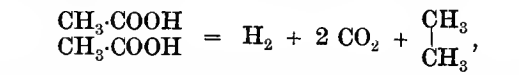
[1] *Ber.* **37**. 2848 (1904). [2] Hantzsch, *Ber.* **37**. 3434 (1904).

This reaction gives bad yields of the lower members of the series owing to the formation of ring compounds, such as pyrrolidine and piperidine; but this ring-formation diminishes, and the yield improves, as the number of carbon atoms increases.[1]

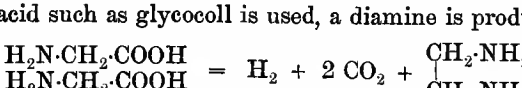
3. By Gabriel's phthalimide reaction:—



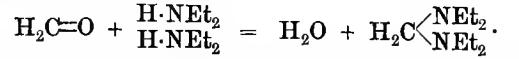
4. By a modification of Kolbe's electro-synthesis. Just as acetic acid on electrolysis gives hydrogen at the cathode and a mixture of carbon dioxide and ethane at the anode:—



so[2] if an amino-acid such as glycocoll is used, a diamine is produced:—

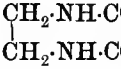


5. The substituted α-diamines may be got by the action of secondary amines on oxymethylene (formaldehyde):—



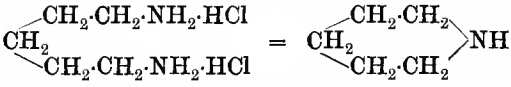
The alkylene diamines are colourless liquids or solids of low melting-point[3]; it is to be noticed that their melting-points, like those of the dibasic acids, rise and fall alternately, so that a compound with an odd number of carbon atoms always melts at a lower temperature than one with one carbon atom less: the boiling-points, however, rise continuously. (The melting-points are: C_2, +8·5°; C_3, liquid; C_4, 27°; C_5, liquid; C_6, 42°.) They are easily soluble in water, and are strong diacid bases, attracting carbon dioxide from the air. They have a great affinity for water; some of them form hydrates with constant boiling-points, which will not give up their water except on heating for several hours with freshly fused potash, or on repeated distillation over sodium: in this they resemble hydrazine.

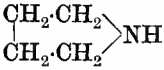
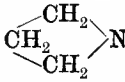
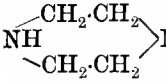
Nitrous acid converts them into glycols, or sometimes, by loss of water from the latter, into unsaturated alcohols. Ethylene diamine itself is converted by nitrous acid into ethylene oxide.

As in the monamines, the amine hydrogen can be replaced by acyl groups. Thus, on shaking the alkaline solution with benzoyl chloride, characteristic dibenzoyl derivatives are produced, such as  . This is the Schotten-Baumann reaction, which is of great importance for isolating and identifying various classes of bodies containing an NH group.

[1] v. Braun, Müller, *Ber.* **38**. 2203 (1905). [2] Lilienfeld, *C.* **04**. i. 133
[3] Kaufler, *C.* **01**. i. 610.

The hydrochlorides of the diamines when heated lose NH_4Cl to give cyclic imines, but with very different ease, and not always in the same way. Pentamethylene-diamine reacts very readily, giving piperidine :—

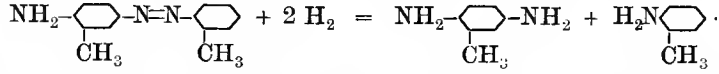


Tetramethylene-diamine gives the corresponding pyrrolidine (tetrahydro-pyrrol)  . Trimethylene-diamine gives a certain quantity of trimethylene-imine,  , but produces mainly picolines (methyl-pyridines) by a more complicated reaction. Ethylene-diamine does not form any ethylene-imine,  , although this body exists, but only diethylene-diimine,  . This is obviously a question of strain in Baeyer's sense, the larger rings being the most easily formed.[1]

Some of these diamines are among the ptomaines found in the animal body a short time after death. Such are tetramethylene-diamine or putrescine and pentamethylene-diamine or cadaverine. They are probably derived from the diamino-acids which are among the constituents of the proteins.

Aromatic diamines

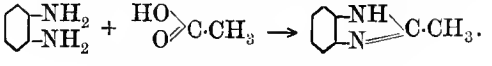
These are most easily formed by the reduction of the dinitro-compounds or the nitro-amines with tin or stannous chloride and hydrochloric acid. They can also be got by the reduction of the aminoazo-bodies, which gives a diamine and a monamine :—



They are colourless crystalline bodies, which are much more soluble in water than the aniline bases. They form salts with two equivalents of acid. They are very easily oxidized ; their solutions are readily acted on by air and light. But the solid diamines and their salts are stable and may be kept without change.

Their chemical behaviour depends largely on the relative position of the two amino-groups.

The ortho-diamines are remarkable for their great tendency to form ortho-condensation-products ; the two nitrogens joining up through the other body with which they react to form a new ring. Thus they combine with acids to form the anhydro-bases, cyclic amidines or imidazoles :—

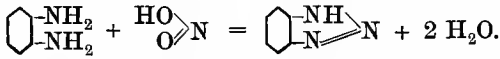


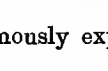
[1] See under trimethylene-imine.

These bodies are strong bases, and are thereby distinguished from the true amides, such as $C_6H_4(NH{\cdot}CO{\cdot}CH_3)_2$, which are formed with acids by the meta- and para-diamines. Such amides are also formed by ortho-diamines if they are treated with acid anhydrides instead of acids, but they are unstable, and when heated above their melting-points readily pass into the anhydro-bases.

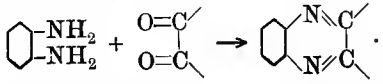
Similar anhydro-bases have been obtained[1] from the fatty diamines also, by heating their hydrochlorides with sodium acetate. In this case a mixture of the anhydro-base and the true amide is produced. The proportion of anhydro-base is greater the less the distance between the amino-groups. Thus trimethylene-diamine gives mainly the anhydro-base, tetramethylene-diamine mainly the amide. These results further support the strain theory, and they at the same time illustrate the greater rigidity of the benzene ring as compared with an open chain; for the aromatic bodies corresponding to tri- and tetramethylene-diamine, namely meta- and para-phenylene-diamine, do not form anhydro-bases at all.

The ortho-diamines form similar ring compounds with nitrous acid, the azimides:—

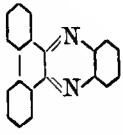


These are colourless excessively stable substances, which can be boiled with acid or alkali or heated to a high temperature without decomposition. They are thus sharply distinguished from the diazo-compounds, and more particularly from the enormously explosive azoimide,  , which contains the same chain of three nitrogen atoms. This difference also is no doubt due to the strain in the ring.

In the same way the ortho-diamines condense with the ortho-(α)-diketones, giving azines or quinoxalines:—

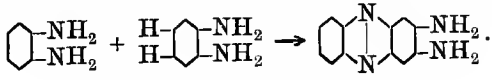


These are formed very easily, and may be used to characterize the ortho-diamines. The alcoholic solution of the diamine is boiled with an acetic acid solution of phenanthrene quinone, when the phenanthrazine

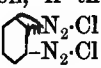


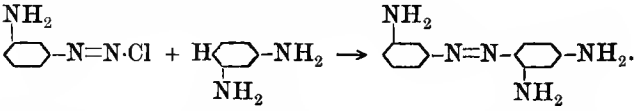
separates at once, and may be identified by its melting-point and by analysis.

Finally, ortho-phenylene-diamine is capable of an ortho-condensation with itself, forming an azine. If its concentrated hydrochloric acid solution is warmed with ferric chloride, long deep red needles of diamino-phenazine separate:—



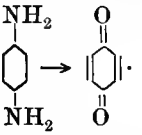
[1] Haga, Majima, *C.* **03.** i. 702.

The meta-diamines are incapable of these condensations to anhydro-bases, azimides, azines, and so forth. Their most characteristic behaviour is with nitrous acid. In strong hydrochloric acid solution, if the nitrous acid is always kept in excess, a normal tetrazo-compound,  , is formed. But if the neutral solution of the hydrochloride is treated with sodium nitrite, a brown dye of the aminoazo-class is produced:—



This is Bismarck brown or Manchester brown, the earliest azo-dye (1866). Owing to this reaction a solution of meta-phenylene-diamine is turned deep yellow by a trace of nitrous acid, a very delicate test for the latter. (It is to be remembered that the best organic test for nitrous acid is meta-phenylene-diamine, and for nitric acid, di-phenylamine.)

The para-phenylene-diamines are distinguished by the ease with which they form quinones:—



Also when treated in dilute acid solution with hydrogen sulphide and ferric chloride they form violet or blue dyes (Lauth's violet).

It is to be noticed that the reactions of the ortho-diamines in giving ortho-condensation-products, and of the para- in giving quinones, are characteristic of the ortho- and para-di-substitution-products respectively in many other cases as well.

Compounds containing more than two amino-groups attached to a benzene nucleus are not of great importance. They may be prepared by nitrating the acetyl-derivatives of the diamines and reducing. In this way compounds up to penta-amino-benzene, $C_6H(NH_2)_5$, have been made. Attempts to prepare hexa-amino-benzene, $C_6(NH_2)_6$, have not been successful. Trinitro-triamino-benzene can be made, but when it is reduced one nitrogen is split off and penta-amino-benzene formed. This looseness of attachment of the nitrogen is characteristic of these poly-amines. Thus triamino-mesitylene, when its hydrochloride is boiled for four hours with acetic acid, has one NH_2 replaced by hydroxyl,[1]

$$C_6(CH_3)_3(NH_2)_3 \longrightarrow C_6(CH_3)_3(NH_2)_2OH.$$

Also, as the number of amino-groups increases, the compounds become more soluble in water, and more unstable and readily oxidized.

QUINONE IMINES AND DIIMINES

These form a group of compounds closely allied to the diamines, which are of considerable theoretical importance. They are derived from the quinones by replacing the oxygen by NH or substituted NH. The first to be prepared

[1] Wenzel, *C.* **02.** i. 185.

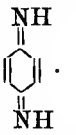
were the chlorimine Cl·N=⬡=O and the dichlorimine Cl·N=⬡=N·Cl. They are got by oxidizing para-amino-phenol and para-phenylene-diamine with bleaching powder. They are respectively yellow and colourless crystalline bodies; they are volatile in steam, and are decomposed by dilute acids to form ammonium salts and quinone.

Many vain attempts were made to obtain the mother substances, the monimine $O{=}C_6H_4{=}NH$, and the diimine $HN{=}C_6H_4{=}NH$, until recently Willstatter[1] succeeded in preparing them in two ways: firstly, by treating the dichlorimine with hydrochloric acid, which acts as a reducing agent (like hydriodic acid), as it does in other cases with chlorine attached to trivalent nitrogen: probably an intermediate addition-compound is formed:—

$$C_6H_4(=NCl)_2 \longrightarrow C_6H_4(=NHCl_2)_2 \longrightarrow C_6H_4(=NH)_2 + 2\ Cl_2;$$

secondly,[2] by oxidizing the amino-phenol or the phenylene-diamine in ethereal solution with silver oxide, or in some cases with lead dioxide.

The bodies are very difficult to isolate, and can only be prepared if the materials are absolutely dry. The best known is the diimine



It is a colourless crystalline substance, whose solutions are colourless at first, though thoy soon become coloured owing to decomposition: its molecular weight in acetone solution (as determined by the boiling-point) is that of the simple formula. It is explosive. It is easily reduced to para-phenylene-diamine, and when treated with dilute acids it breaks up into ammonia and quinone. It is not acidic but is weakly basic, forming a colourless hydrochloride.

The monimine, $O{=}C_6H_4{=}NH$, is similar, and is also colourless; but it is even less stable, and explodes spontaneously in a few minutes.

By the oxidation of the methyl-*p*-phenylene-diamines Willstätter[3] obtained the methyl- and dimethyl-diimines, which likewise are colourless and explosive:—

$$CH_3N{=}C_6H_4{=}NH \quad \text{and} \quad CH_3N{=}C_6H_4{=}NCH_3.$$

The absence of colour in these compounds is important, in view of their undoubtedly quinoid structure. It is commonly assumed that all quinoid compounds are coloured, like the quinones themselves: and there is even a tendency to suppose that nearly all coloured aromatic derivatives contain a quinoid ring. But these views require to be reconsidered in view of the recent discoveries on the one hand of quinoid substances (like the imines) which are colourless, and on the other of coloured bodies closely resembling the (supposed quinoid) aromatic coloured compounds, which cannot contain a quinoid ring because they are not aromatic derivatives at all.

The causes which determine the absence of colour among these quinone derivatives are not understood. It seems certain that the simple quinoid

[1] Willstätter, Mayer, *Ber.* **37**. 1494 (1904).
[2] Willstätter, Pfannenstiehl, *Ber.* **37**. 4605 (1904).
[3] *Ber.* **38**. 2244 (1905).

compounds form two series, one coloured, like the quinones themselves, and the other not. On the other hand, these bodies are capable of a further increase of colour, which must be accompanied by some structural change. In the triphenyl-methane series, for example, the feebly coloured Homolka bases go over on treatment with acids into the brilliantly coloured dyes. This is generally represented as the passage of trivalent into pentavalent nitrogen:—

$$(H_2N\cdot C_6H_4)_2C{=}\langle\rangle{=}NH \longrightarrow (H_2N\cdot C_6H_4)_2C{=}\langle\rangle{=}NH_2Cl.$$

But there is much evidence to show that the change of valency of the nitrogen is not sufficient to determine colour: thus the diimine salts are colourless. It is clear that the influence of a pentavalent nitrogen atom on the colour largely depends on whether it still has a hydrogen atom attached to it: if it has, then the effect on the colour is much the same as if it was trivalent; if it has not, then its effect is usually quite different.[1] The conversion of the group $-NX_2$, where X is a hydrocarbon radical, into $-NX_2HCl$ does not seem in general to influence the colour, but its conversion into $-NX_3Cl$ does so in a very marked way. Of this we have an example in the quinone imine derivatives which we have just been considering, and another (curiously in the opposite direction) in the rosaniline dyes, where the change from $-NEt_2$ to $-NEt_2HCl$ is without effect, while the change to $-NEt_3Cl$ destroys the influence of this group on the colour altogether. This is one of the phenomena which suggest that there is a difference in constitution between bodies of the type R_3NHX and those of the type R_4NX.[2]

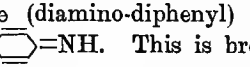
We must therefore look for some other change of structure in the conversion of the Homolka bases into the rosaniline dyes. In this connexion certain facts recently discovered by Willstätter[3] with regard to the quinone-diimines are of great interest. If unsymmetrical dialkyl-*p*-phenylene-diamine is oxidized, brilliantly coloured substances are produced, known from their discoverer as Wurster's salts, which were supposed to be true diimine derivatives, e. g. $HN{=}C_6H_4{=}N(CH_3)_2Cl$. Further investigation has shown, however, that these bodies contain an atom of hydrogen more than this: they are bimolecular compounds (analogous to the quinhydrones) of one molecule of the oxidation product with one molecule of the unoxidized diamine, and may be written

$$\begin{array}{ll} NH_2Cl\ldots\ldots\ldots\ldots NH_2 & \\ \| \qquad\qquad\qquad\quad | & \\ C_6H_4 \qquad\qquad\quad C_6H_4 & , \\ \| \qquad\qquad\qquad\quad | & \\ N(CH_3)_2Cl\ldots\ldots N(CH_3)_2 & \end{array}$$

the dotted lines indicating some unknown kind of linkage. If they are further oxidized to the true diimines the colour disappears. Willstätter suggests that this peculiar linkage, which he calls meri-quinoid (partially quinoid), is the cause of colour in bodies of this type. An analogous explanation would hold for the triphenyl-methane dyes, the true dye having a linkage between the quinoid nucleus and one of the other nuclei, which would be absent in the Homolka base.

[1] Cf. Pringsheim, *Ber.* **38.** 3354 (1905). [2] See p. 26.
[3] Willstätter, Piccard, *Ber.* **41.** 1458, 3245 (1908): **42.** 1902 (1909).

When *o*-phenylene-diamine is oxidized with silver oxide or lead dioxide it appears to give an *o*-quinone diimine,[1]  , though this is too unstable to be isolated. It gives a yellow solution with a red fluorescence (ortho-benzoquinone itself is red and not yellow).

Benzidine (diamino-diphenyl) seems to give an analogous compound,[2]  . This is brown and gives dark yellow solutions. The chlor-imines, which are more stable and can be isolated, are similar.[3] But the diphenoquinone, $O{=}C_6H_4{=}C_6H_4{=}O$, from which it is derived is itself red in one form, and generally resembles ortho- rather than para-benzoquinone.

The analogous salts from tetramethyl-benzidine, where the nitrogen is pentavalent and has no hydrogen attached to it, form two series, one yellow or red, the other green. The red salts probably have the formula

$$(CH_3)_2\underset{Cl}{\diagdown}N{=}C_6H_4{=}C_6H_4{=}N\underset{Cl}{\diagup}(CH_3)_2.$$

The benzidine compounds are able, like the *p*-phenylene diamines, to give coloured 'meri-quinoid' oxidation products.[4]

[1] Willstätter, Pfannenstiehl, *Ber.* **38.** 2348 (1905).
[2] Willstätter, Kalb, *Ber.* **37.** 3761 (1904); **38.** 1232 (1905).
[3] Schlenk, *Ann.* **363.** 313 (1908). [4] Schlenk, l. c.

CHAPTER IV

AMIDES

As the amines are formed by replacing the hydrogen of ammonia by hydrocarbon radicals, so by replacing it by acid radicals the amides are produced: or we may say that the amines are alcohols whose hydroxyl is replaced by NH_2, and the amides acids whose hydroxyl is replaced by NH_2. As in the case of the amines, primary, secondary, and tertiary amides exist; but the last two classes are of small importance. Quaternary amides are unknown.

Methods of formation

1. By heating the ammonium salts of the acids:—

$$CH_3{\cdot}C\langle^{O}_{O{\cdot}NH_4} = H_2O + CH_3{\cdot}C\langle^{O}_{NH_2}\cdot$$

This reaction is exactly parallel to the formation of ester from acid and alcohol, as is evident if they are written:—

$$(a)\quad CH_3{\cdot}C\langle^{O}_{OH} + HNH_2 = H_2O + CH_3{\cdot}C\langle^{O}_{NH_2}\cdot$$

$$(b)\quad CH_3{\cdot}C\langle^{O}_{OH} + HO{\cdot}C_2H_5 = H_2O + CH_3{\cdot}C\langle^{O}_{OC_2H_5}\cdot$$

The similarity is not merely formal. Goldschmidt[1] has investigated the rate of formation of substituted amides (anilides) and finds that it follows the same laws as esterification. In both cases the reaction in the absence of a strong acid is bimolecular, being auto-catalysed by the hydrogen ion of the organic acid itself. In the presence of a strong acid it is highly catalysed, and then becomes monomolecular, as the disappearance of the organic acid no longer diminishes the concentration of the hydrogen ion.

This work has been confirmed by Menschutkin,[2] who has investigated the influence of the nature of the organic acid on the velocity, and on the percentage of amide formed when equilibrium is reached. (These experiments, like Goldschmidt's, were carried out by dissolving the acid in a large excess of the amine, under which conditions the reaction is far from complete.) Menschutkin's general conclusions are that the velocity is greatest with normal fatty acids. The presence of branch chains diminishes it, and the more so the nearer they are to the carboxyl. With the true aromatic acids (where the carboxyl is directly attached to the nucleus) the velocity is very small, as it is with all acids which have the carboxyl attached to a tertiary carbon atom. Side chains on the nucleus diminish the velocity greatly in the ortho position: in the meta and para they sometimes increase it. Aromatic acids whose carboxyl is in the side chain behave like fatty acids.

[1] *Z. Ph. Ch.* **24.** 353 (1897).

[2] *C.* **03.** i. 1121; ii. 324.

The case of the ortho and di-ortho-substituted benzoic acids is of interest. V. Meyer has laid down the general rule that the reactions of benzoic acid and its derivatives are in general delayed or prevented by the presence of two (and in less degree of one) ortho-substituents. In accordance with this Menschutkin finds that the rate of formation of the amides is diminished by the presence of an ortho-substituent: the case of two he has not examined. But it does not follow that the percentage of amide present at equilibrium will be diminished. It is characteristic of stereo-hindrance in general, and of this form of it in particular, that where it delays a reaction it also delays the reverse action. Thus it hinders not only the formation of the esters but also their saponification. In fact stereo-hindrance is of the nature of a negative catalyst. It acts not by causing instability of the product (as a purely chemical influence does) but by making a particular group difficult of access. Hence not only is the group slow to react, but the product of its reaction is slow to decompose. Since, however, the proportions at equilibrium do not depend on either of these reaction-velocities separately, but on the ratio between them, they are much less affected by the stereo-hindrance, and need not necessarily be affected by it at all. These general principles are well illustrated by the case under consideration, that of the amides. That the velocity of hydrolysis of benzamide is greatly diminished by ortho-substituents has been shown by Sudborough.[1] The percentage of monobrom-benzamide hydrolysed by boiling for 15 minutes with 30 per cent. sulphuric acid was: ortho 25·07, meta 99·2, para 80·7. With the di-ortho-substituted compounds the effect was so great that a more energetic treatment was required. After heating for 7 hours to 160° with 75 per cent. sulphuric acid, di-*o*-dibrom-benzamide was only hydrolysed to the extent of 11·56 per cent.: whereas under the same conditions over 99 per cent. of *o-p*-dibrom-benzamide is broken up. In the same way Menschutkin's results show that while ortho-substituents greatly diminish the initial velocity of amide-formation they have much less effect on the percentage formed at equilibrium, which may even be increased: the following are the numbers obtained for *o*- and *m*-toluic acid, with ammonia and dimethylamine respectively:—

	With NH_3		With $NH(CH_3)_2$	
	Initial velocity	Per cent. at equilibrium	Initial velocity	Per cent. at equilibrium
o-toluic acid	29·1	83·4	19·4	74·3
m-toluic acid	56·4	78·5	26·4	64·1

The hydrolysis of amides both by acids and by alkalies in aqueous solution has been measured by Crocker,[2] who determines the extent to which the reaction has gone by means of the conductivity. In both cases the reaction is shown to be bimolecular, i. e. the velocity is proportional to the product of the concentrations of the amide and the acid or the alkali. The catalytic effect of hydroxyl ion is much greater than that of hydrogen ion.

[1] *J. C. S.* **1897**, 229.

[2] Crocker, *J. C. S.* **1907**. 593; Crocker, Lowe, ib. 952. Cf. Davis, *J. C. S.* **1909**. 1397.

This reaction for forming the amides, by heating the ammonium salt, or a mixture of the acid and the amine, is the one most commonly used. The dry ammonium salt cannot be made by evaporating down the aqueous solution without great loss, as it dissociates. It is therefore usually prepared by saturating the anhydrous acid with ammonia or ammonium carbonate. The dry salt can then be distilled: but if so, there is much loss through dissociation into ammonia and acid. It is better to heat it in sealed tubes to about 230° for several hours: from the product, in the case of the lower acids, the amide is separated by distillation; in the case of the higher, it is found crystallized out.

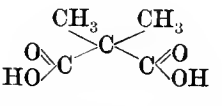
It was by this method that the first known amide, oxamide, was prepared by Dumas in 1830.

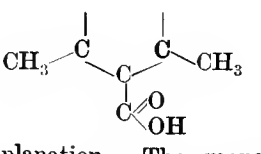
2. From the esters by the action of aqueous ammonia: this was used by Liebig in 1834 for making oxamide:—

$$\begin{matrix} O{=}C{\cdot}OC_2H_5 \\ O{=}C{\cdot}OC_2H_5 \end{matrix} + \begin{matrix} NH_3 \\ NH_3 \end{matrix} = \begin{matrix} O{=}C{\cdot}NH_2 \\ O{=}C{\cdot}NH_2 \end{matrix} + \begin{matrix} HO{\cdot}C_2H_5 \\ HO{\cdot}C_2H_5 \end{matrix}.$$

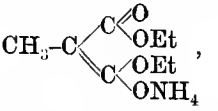
This goes well with the lower and more soluble esters, such as formic, acetic, and oxalic, sometimes even in the cold: the higher esters must be heated in sealed tubes, and the yields are not good.

An interesting case of the failure of this reaction, apparently for stereochemical reasons, has been discovered by E. Fischer.[1] Malonic ester easily forms its diamide, $CH_2(CO{\cdot}NH_2)_2$, when treated with aqueous ammonia in the cold. The mono-alkyl-malonic esters form their diamides (such as $C_3H_7CH(CO{\cdot}NH_2)_2$) almost but not quite as easily. But the esters of dialkyl-malonic acid, even of dimethyl-malonic acid, $(CH_3)_2C(COOH)_2$, can only be got to yield amides with the greatest difficulty, and sometimes not at all. This is the more remarkable since the chloride of dimethyl-malonic acid reacts with ammonia with the greatest ease to give a perfectly stable diamide, $(CH_3)_2C(CO{\cdot}NH_2)_2$. This case has an obvious resemblance to that of the di-ortho-substituted benzoic acids, and may probably be explained in the same way:—





Fischer, however, suggests a different explanation. The monalkyl-malonic esters, like malonic ester itself, contain an acidic hydrogen atom, while the dialkyl do not: and this may possibly be the cause of the inactivity of the latter. Fischer supposes that the ammonia first forms a salt with the tautomeric form of the ester



which then loses alcohol to give the amide. Of course a dialkyl-malonic ester could form no such derivative. The explanation is ingenious, but it can hardly be maintained. In the analogous case of the benzoic acids no such

[1] *Ber.* **35**. 844 (1902).

explanation is possible, whereas stereo-hindrance is a well established influence, which is quite sufficient to account for the facts. It seems probable that in these cases of amide-formation there are two influences at work, a chemical influence and that of stereo-hindrance. It is the latter, for example, which prevents the formation[1] of the amide from the ester of trimethyl-acetic acid, and the former which causes it to be produced easily from that of trichloracetic acid.

3. The action of ammonia or amines on the acid chloride or acid anhydride:—

$$(CH_3\cdot CO)_2O + 2\,NH_3 = CH_3\cdot CO\cdot NH_2 + CH_3\cdot CO\cdot ONH_4$$
$$CH_3\cdot CO\cdot Cl + 2\,NH_3 = CH_3\cdot CO\cdot NH_2 + NH_4Cl.$$

By this reaction Liebig and Wöhler in 1832 prepared benzamide from benzoyl chloride. With the higher acids it is better to use the acid chloride.

If one molecule of acid chloride is treated with one molecule of each of two amines, the amide of the more negative amine is produced and the hydrochloride of the more positive.[2]

To this reaction is probably to be referred a singular method of preparing amides discovered by Orton.[3] This consists in treating a dilute ammoniacal solution of the acid with benzoyl chloride, and shaking with soda till the smell of the benzoyl chloride disappears, when the amide separates mixed with a certain quantity of benzamide. It seems probable that the benzoyl chloride reacts with the acid either to give the acid chloride or to give the acid anhydride, and then this acid chloride or anhydride acts on the ammonia to form the amide. It is remarkable that unless excess of ammonia is used the amount of benzamide formed is very small.

All these methods may be used for preparing alkylated amides by substituting alkylamines for ammonia, and for the aromatic derivatives by using the anilines.

4. By the addition of water to the nitriles:—

$$CH_3\cdot C{\equiv}N + H_2O = CH_3\cdot CO\cdot NH_2.$$

This may be done by dissolving them in concentrated sulphuric acid, by shaking them with concentrated hydrochloric acid, or most easily by the action of hydrogen peroxide in alkaline solution:—

$$C_5H_{11}\cdot C{\equiv}N + 2H_2O_2 = C_5H_{11}\cdot CO\cdot NH_2 + O_2 + H_2O.$$

This is a remarkable reaction, as it appears to be due to the nascent water.

5. Alkylated amides can also be obtained by the action of acids on isocyanic esters (as water gives amines):—

$$CH_3\cdot COOH + C_2H_5N{=}C{=}O = CH_3\cdot CO\cdot NHC_2H_5 + CO_2.$$

Properties of the amides

All the amides except formamide are crystalline solids. The lower are excessively soluble in water and are deliquescent: they can be distilled un-

[1] H. Meyer, *Mon.* **27**. 31 (*C.* **06**. i. 1235).

[2] Dains, *J. Am. Ch. Soc.* **28**. 1183 (*C.* **06**. ii. 1186).

[3] *J. C. S.* **1901**. 1352.

changed. They generally have an unpleasant smell, but this is due to impurities. Pure acetamide (like pure iodoform and pure skatole) has no smell.

Though the amines have much lower boiling-points than the corresponding alcohols, the amides boil at much higher temperatures than the acids from which they are derived. Thus acetic acid boils at 118°, acetamide at 223°: the difference diminishes in ascending the series.

The amides are comparable in constitution to the primary amines, but differ from them markedly in behaviour. The electro-negative acyl group makes them indifferent substances of neutral reaction. The basic character of the NH_2 group is not wholly destroyed, and they are able to form salts with strong acids: but these have a strongly acid reaction and are highly hydrolysed. The alkylated amides are more basic and can give stable platinichlorides. In consequence of the more negative character of the amides as compared with the amines, the hydrogen is more easily replaced by metals. Thus an aqueous solution of an amide dissolves mercuric oxide, and on evaporation salt-like bodies such as $Hg(NH{\cdot}CO{\cdot}CH_3)_2$ crystallize out. This is the general behaviour of NH attached to negative groups, as shown in isocyanic acid, $H{\cdot}N{=}C{=}O$, and in phthalimide.

This formation of salts raises the question of the true formula of the amides. Besides that which has been hitherto assumed, there is the possibility of the tautomeric formula of an iso-amide or imino-hydrin:—

$R{\cdot}C\langle^{O}_{NH_2}$ Normal amide $R{\cdot}C\langle^{OH}_{NH}$ Iso-amide

Alkyl derivatives of both forms are known. Those of the first are the normal alkyl-amides, those of the second are the so-called imino-ethers. They can both be obtained from, and converted into, the normal amides, whose behaviour is thus to some extent tautomeric. But the balance of evidence with regard to the free amides is strongly in favour of the first (normal) formula. This conclusion is arrived at by Auwers[1] from their cryoscopic behaviour; by Claisen[2] from a comparison with the oxymethylene compounds; by Schmidt[3] from spectroscopic investigations; and by Hantzsch[4] from the fact that they do not form salts with ammonia in non-dissociating solvents, as bodies with an acidic hydroxyl group would be expected to do.

The structure of the metallic derivatives is much less easy to determine. It is quite conceivable that while the free amides have the normal structure, their salts may be derived from the iso-formula $R{\cdot}C\langle^{OM}_{NH}$, the metal going, as it so often does, into the more acidic position. The evidence is not conclusive. The mercury compounds appear to be the normal N-salts, $R{\cdot}CO{\cdot}NHhg$.[5] They have the tendency, characteristic of compounds containing mercury joined to nitrogen, not to dissociate in water; and hence their solutions give very few of the reactions of the mercuric ion. But this is very little guide to the constitution

[1] *Ber.* **34.** 3558 (1901). [2] *Ann.* **287.** 360 (1895). [3] *Ber.* **36.** 2459 (1903).
[4] *Ber.* **35.** 226 (1902). [5] Ley, Schäfer, *Ber.* **35.** 1309 (1902).

of the salts of other metals, as we know that mercury has a very strong tendency to combine with nitrogen. The silver salts generally give O-ethers (imino-ethers) when the metal is replaced by alkyl, and have therefore been assumed to be iso-salts $R{\cdot}C\langle^{OAg}_{NH}$. But there is plenty of evidence to show how untrustworthy this reaction (the replacement of the metal by alkyls) is for determining the constitution of metallic derivatives. It seems probable that the silver salts can exist in two isomeric forms. Thus Titherley[1] has shown that besides the ordinary white silver benzamide, which gives imino-ethers, and so may possibly be $\phi{\cdot}C\langle^{OAg}_{NH}$, there is an orange silver salt, formed by the action of alcoholic silver nitrate on potassium benzamide, which may be $\phi{\cdot}C\langle^{O}_{NHAg}$.

The structure of the alkaline salts is equally uncertain. Those of the aromatic amides react readily with alkyl iodides to give O-ethers, while those of the fatty amides will hardly react at all. This certainly seems to indicate that there is a difference of constitution between them: and Titherley considers that the alkaline salts of the aromatic amides are O-salts, $Ar{\cdot}C\langle^{ONa}_{NH}$, while those of the fatty amides are N-derivatives, as $CH_3{\cdot}C\langle^{O}_{NHNa}$. But the question cannot yet be regarded as settled.

One of the most marked differences between the amides and the amines is that the nitrogen is much less firmly attached to the carbon in the amides. (It is a general rule that an increase in the negative character of a molecule weakens the linkages within it. Compare for the C-O-C grouping, the ethers, esters, and acid anhydrides: for C-C, such cases as oxalic and trichloracetic acids, &c.) The amides can be saponified even by heating with water, their formation from acid and ammonia being, as has been mentioned, a reversible reaction: and much more easily by acids and alkalies. This reaction has been used by Ostwald to measure the concentration of hydrogen ion, that is, the strength of acids.

A similar reaction occurs when the amides are heated with alcohols. In this case the reaction may go in two ways: the alcohol radical may attach itself either to the acid or to the nitrogen:—

$$CH_3{\cdot}C\langle^{O}_{NH_2} + C_2H_5OH \rightarrow \begin{cases} CH_3{\cdot}C\langle^{O}_{OH} + C_2H_5NH_2 \\ CH_3{\cdot}C\langle^{O}_{OC_2H_5} + NH_3 \end{cases}$$

As a matter of fact both reactions occur.

The hydrolysis of the amides by certain natural ferments, such as pepsin and trypsin, has already been mentioned in discussing the polypeptides; it is not confined to those amino-acid derivatives, but is shared by the simple amides.[2]

With dehydrating agents such as phosphorus pentoxide the amides give

[1] *J. C. S.* **1897.** 468; **1901.** 391.

[2] Gonnermann, *C.* **02.** i. 909; **03.** i. 960.

nitriles. This makes it possible to go both ways along the series of reactions:—

$$CH_3{\cdot}C\langle^{O}_{ONH_4} \underset{\text{heat}}{\overset{\text{boiling water}}{\rightleftharpoons}} CH_3{\cdot}C\langle^{O}_{NH_2} + H_2O \underset{P_2O_5}{\overset{H_2SO_4 \text{ or } H_2O_2}{\rightleftharpoons}} CH_3{\cdot}C{\equiv}N + 2\,H_2O.$$

The simpler fatty amides, like acetamide, when acting as solvents behave somewhat like water. Pure acetamide is a conductor of electricity, and is no doubt ionized to a small extent. Solutions of salts in acetamide also conduct,[1] though to a less extent than in water. In the same way the salts of weak bases are 'amidolysed' by formamide, just as they are hydrolysed by water.[2] For example, antimony trichloride dissolved in formamide gives a white precipitate composed of a mixture of $SbCl_2X$, $SbClX_2$, and SbX_3, where X = NH·CHO. So, too, it can combine with salts, acting like water of crystallization.[3] In solution the amides are commonly associated, some of them even in water.[4]

The conversion of the amides by the action of alkali and bromine into the amines has already been mentioned as a mode of preparing the latter. The various stages of this singular reaction have now been made out. The amide is first treated with bromine and potash (commercially chlorine and potash or chlorine and soda are used), whereby it is converted into the monobromamide:—

$$CH_3{\cdot}C\langle^{O}_{NH_2} + Br_2 = CH_3{\cdot}C\langle^{O}_{NHBr} + HBr.$$

This is a very reactive substance. If it is treated with ammonia or aniline a violent reaction occurs, and the amide is regenerated. The bromine atom increases the acidity of the amide, so that the remaining hydrogen atom is more easily replaced by metals. Hantzsch[5] has shown that the bromamide is a pseudo-acid: that is to say, though it is not itself an acid it gives with bases the salts of an acidic tautomeric form, the iso-amide. Thus the potash with which it is treated in the Hofmann reaction forms the potassium salt of the iso-bromamide, $CH_3{\cdot}C\langle^{OK}_{NBr}$ The alkaline liquid is then distilled, when the following changes take place. In the first place the potassium salt contains the peculiar C=N linking, which also occurs in the oximes. Now the oximes are capable of undergoing the Beckmann reaction, whereby they are converted into the amides:—

$$\begin{matrix}\phi{\cdot}C{\cdot}H \\ \| \\ HO{\cdot}N\end{matrix} \rightarrow \begin{matrix}HO{\cdot}C{\cdot}H \\ \| \\ \phi{\cdot}N\end{matrix} \rightarrow \begin{matrix}O{=}C{\cdot}H \\ | \\ \phi{\cdot}N{\cdot}H\end{matrix},$$

benzaldoxime giving formaldehyde. The essence of this reaction, which involves a very unusual insertion of a nitrogen atom into the middle of a carbon chain, is that the two groups on the same side of the C=N change places. We may suppose the same change to occur with the similarly constituted potassium salt of the bromamide:—

$$\begin{matrix}CH_3{\cdot}C{\cdot}OK \\ \| \\ Br{\cdot}N\end{matrix} = \begin{matrix}Br{\cdot}C{\cdot}OK \\ \| \\ CH_3{\cdot}N\end{matrix} = KBr + \begin{matrix}C{=}O \\ \| \\ CH_3{\cdot}N\end{matrix}.$$

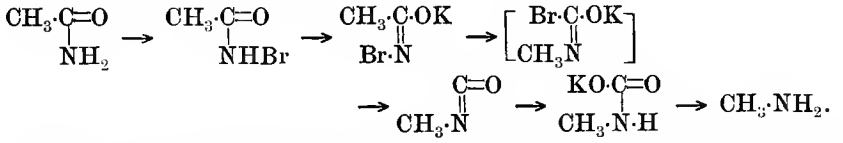
[1] J. W. Walker, Johnson, *J. C. S.* **1905.** 1597.
[2] Bruni, Manuelli, *Z. f. Elektrochem.* **11.** 554 (*C.* **05.** ii. 873).
[3] Menschutkin, *C.* **09.** i. 909.
[4] Meldrum, Turner, *J. C. S.* **1908.** 876.
[5] *Ber.* **35.** 226, 3579 (1902).

In the primary product the bromine and the potassium are on the same carbon atom, and they therefore split off together as potassium bromide, leaving an isocyanate. If the bromamide is treated with silver carbonate the isocyanate can actually be isolated; but in the ordinary Hofmann reaction, where excess of alkali is used, it cannot be detected, and its formation has been denied. It has, however, been shown[1] that if the bromamide is treated with one equivalent of alkali, and the solution distilled with steam, the isocyanate passes over. If the alkali is in excess, the isocyanate does not appear as such, but is immediately transformed, through the intermediate stage of the carbamate, into the amine and carbon dioxide:—

$$R{\cdot}N{=}C{=}O + KOH \longrightarrow R{\cdot}NH{\cdot}CO{\cdot}OK \longrightarrow R{\cdot}NH_2 + CO_2.$$

At the same time (and especially if the alkali is not in excess) some of this amine reacts with the unchanged isocyanate to form the di-substituted urea $CO(NH{\cdot}R)_2$.

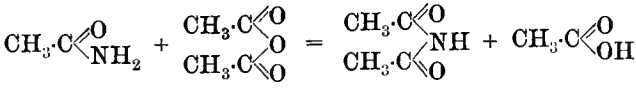
Thus Hantzsch's discovery of the constitution of the bromamide salts supplied the link necessary to the explanation of this remarkable reaction, by establishing its exact analogy to the Beckmann reaction. To recapitulate, the following changes take place, in which all the stages except the one in brackets have been isolated:—



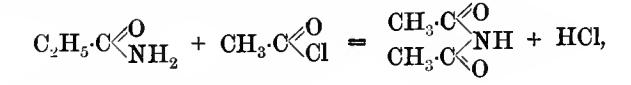
There is a remarkable method, not fully understood, of forming the amide of phenyl-acetic acid and its homologues. It consists in acting on the mixed fatty-aromatic ketones with yellow ammonium sulphide. Thus acetophenone is converted into phenyl-acetamide:—

$$\phi{\cdot}CO{\cdot}CH_3 \longrightarrow \phi{\cdot}CH_2{\cdot}CO{\cdot}NH_2.$$

The secondary and tertiary amides, such as diacetamide, $NH(CO{\cdot}CH_3)_2$, may be got by boiling the primary amides with an acid anhydride:—



or by acting[2] on the monamides with acid chlorides; this method can be used for preparing the mixed secondary amides:—



or by heating a nitrile with an acid:—

$$CH_3{\cdot}C{\equiv}N + CH_3{\cdot}CO{\cdot}OH = (CH_3{\cdot}CO)_2NH.$$

They are unstable bodies, which easily lose one acyl group on hydrolysis, passing back into the primary amides.

[1] Mohr, *J. Pr. Ch.* (2) **72**. 297; **73**. 177, 228 (*C.* **05**. ii. 1534; **06**. i. 1091, 1153).
[2] Tarbouriech, *C.* **03**. ii. 552, 712.

AMIDES OF DIBASIC ACIDS

These may be of two kinds, according as one or both of the hydroxyls are replaced by NH_2. Bodies of the former kind, which still contain a carboxyl group, are known as -amic acids (oxamic, succinamic, &c.). Thus if acid ammonium oxalate is heated, the monamide, oxamic acid, is formed:—

$$\begin{matrix} O{=}C{\cdot}OH \\ | \\ O{=}C{\cdot}ONH_4 \end{matrix} = \begin{matrix} O{=}C{\cdot}OH \\ | \\ O{=}C{\cdot}NH_2 \end{matrix} + H_2O.$$

This is a white powder, slightly soluble in water. It is an acid, and hence can give salts and esters. If its ethyl ester, known as oxamethane, is heated with phosphorus pentoxide, it loses water and forms cyan-carbonic ester:—

$$\begin{matrix} O{=}C{\cdot}NH_2 \\ | \\ O{=}C{\cdot}OEt \end{matrix} = \begin{matrix} C{\equiv}N \\ | \\ O{=}C{\cdot}OEt \end{matrix} + H_2O.$$

On the other hand, if neutral ammonium oxalate is heated, or if ethyl oxalate is treated with ammonia, the diamide, oxamide, $\begin{matrix} O{=}C{\cdot}NH_2 \\ | \\ O{=}C{\cdot}NH_2 \end{matrix}$, is produced. This is a crystalline almost insoluble powder, which on heating to a rather high temperature sublimes partly unchanged, partly with decomposition into water and cyanogen. This last change takes place readily and completely if oxamide is heated with phosphorus pentoxide:—

$$\begin{matrix} O{=}C{\cdot}NH_2 \\ | \\ O{=}C{\cdot}NH_2 \end{matrix} = \begin{matrix} C{\equiv}N \\ | \\ C{\equiv}N \end{matrix} + 2\ H_2O.$$

The insolubility and high melting-point of oxamide point to its having a high molecular weight: and this is confirmed by measurements of its molecular weight in solution,[1] which give values nearly twice that of the simple formula.

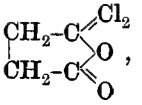
The diamide of succinic acid is remarkable for existing in two forms. When the ester is treated with ammonia the normal diamide, $\begin{matrix} CH_2{\cdot}CO{\cdot}NH_2 \\ | \\ CH_2{\cdot}CO{\cdot}NH_2 \end{matrix}$, is produced. This body loses ammonia with singular ease to form a ring compound, succinimide:—

$$\begin{matrix} CH_2{-}C{<}^{O}_{NH_2} \\ | \\ CH_2{-}C{<}^{NH_2}_{O} \end{matrix} = NH_3 + \begin{matrix} CH_2{-}C{<}^{O}_{} \\ | \\ CH_2{-}C{<}^{}_{O} \end{matrix}\!\!>NH.$$

The ease with which this reaction takes place no doubt depends on the stability of the 5-ring produced, and may be compared with the ease with which succinic acid itself forms an anhydride.

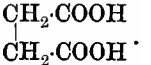
The isomeric diamide is got by the action of ammonia on succinyl chloride. The only structure possible for it is $\begin{matrix} CH_2{-}C{-}NH_2 \\ | \quad\quad\ \backslash O \\ CH_2{-}C{<}_{O} \end{matrix}$, which indicates that the

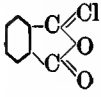
[1] Maselli, *Gaz.* **37**. ii. 135 (*C.* **07**. ii. 1234).

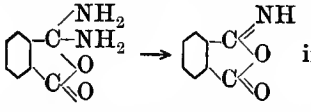
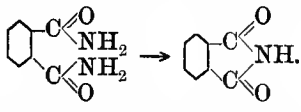
chloride is  , a formula supported also by other evidence.

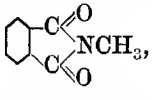
In ordinary (ortho) phthalic acid the relative position of the two carboxyls is the same as in succinic acid :—


o-phthalic acid


Succinic acid

Accordingly the acid shows the same tendency to form an anhydride; and here too there is reason to think that the chloride has the unsymmetrical formula  . If so, the diamide got from it should also be unsymmetrical, and so should the imide, phthalimide, which is readily obtained from the diamide :—

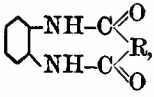

instead of


In this case only one of the two theoretically possible diamides is known, and we cannot tell for certain which of the two formulae should be assigned to it. Phthalimide forms a potassium derivative (which has already been mentioned in discussing Gabriel's amine synthesis), and this when treated with methyl iodide certainly gives a symmetrical methyl-phthalimide  , which is in favour of the view that the imide, and therefore also the diamide, has a symmetrical structure. On the other hand, we have by this time plenty of evidence to show that conclusions as to the structure of tautomeric compounds drawn from the behaviour of their metallic derivatives must be received with great caution. The question must therefore be left open. The most we can say is that in the case of phthalyl chloride the evidence is in favour of an unsymmetrical, and in that of the diamide and imide it is in favour, though more doubtfully, of a symmetrical structure.

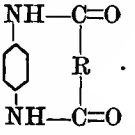
The monamide of amino-succinic (aspartic) acid, $\begin{matrix}CH_2\cdot CO\cdot NH_2\\ |\\ CHNH_2\cdot CO\cdot OH\end{matrix}$, which is known as asparagine, occurs in nature in germinating seeds, in two forms, a dextro and a laevo, which do not racemize but crystallize separately. The interesting point about them is that while the ordinary (laevo) form is tasteless, the dextro is sweet. Now it is only bodies which themselves contain an asymmetric carbon atom—optically active bodies—which can react differently with two optical antimers. Hence Pasteur has said that in this case the nerve substance of the tongue acts as an optically active body.

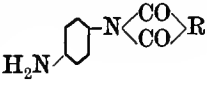
The formation of cyclic diamides[1] from the dibasic acids and the phenylene

[1] R. Meyer, *Ann.* **347.** 17 (1906).

diamines is of some interest. The ortho-diamines give diamides of the type  , with all the dibasic acids from oxalic, which gives a 6-ring, to sebacic, which gives a 14-ring. There is some indication that as the ring gets larger it is formed with more difficulty.

Meta and para-diamines might form compounds of the same type, such as



But in no case are such bodies produced. Instead, only one NH_2 is attacked, and a cyclic imide  is formed.

ANILIDES

These are a class of substituted amides of considerable importance in which one amide hydrogen is replaced by phenyl. They are derived from aniline in the same way as the ordinary amides are derived from ammonia.

They are made by heating aniline with the acid. A salt is no doubt formed at first, and then this breaks up with loss of water, as an ammonium salt does to form an amide, but generally with much more ease.

$$CH_3{\cdot}C\langle{}^{O}_{O{\cdot}NH_3\phi} = H_2O + CH_3{\cdot}C\langle{}^{O}_{NH\phi}\cdot$$

Menschutkin[1] has measured the velocity of formation of acetanilide in acetic acid. He finds it to be bimolecular in the absence of a catalyst; but in the presence of a halogen salt of aniline as catalyst it becomes monomolecular, the iodide having the greatest accelerating effect, and the chloride the least. Ortho substituents on the aniline diminish the velocity, while meta and para greatly increase it. H. Goldschmidt[2] and his pupils have shown that the same results are obtained if the reaction is carried on at 110° in presence of excess of amine. They find that with different acids the ratio of the velocities with any amine is approximately—

Formic	Acetic	Propionic	Butyric	Isobutyric
1000	1	0·5	0·3	0·1

The reaction of aniline with any acid is from two to three times as quick as that of ortho-toluidine.

Formanilide is rapidly produced even if dilute formic acid is boiled with aniline. To prepare acetanilide the anhydrous acid must be used. In making this compound, even in the laboratory, it is convenient to use a reverse air condenser with a side tube at the top. The liquid is boiled at such a rate

[1] *C.* **06.** i. 551; cf. **03.** ii. 324.

[2] Goldschmidt, Wachs, *Z. Ph. Ch.* **24.** 353 (1897); Goldschmidt, Bräuer, *Ber.* **39.** 97 (1906).

that the top of the condenser keeps at 100–110°. The water formed in the reaction distils over with a very small quantity of acetic acid; the concentration of the liquid is thus kept up, and the reaction goes much more rapidly. This method is also used on the large scale.

A curious modification of this reaction is to use instead of the acid the thio-acid, for example thioacetic acid, $CH_3{\cdot}CO{\cdot}SH$. The reaction is similar to that of the acid itself, but sulphuretted hydrogen is formed instead of water:—

$$CH_3{\cdot}C\langle^{O}_{SH} + HNH\phi = CH_3{\cdot}C\langle^{O}_{NH\phi} + H_2S,$$

and this is evolved, instead of remaining in solution and retarding the reaction.

The anilides can also be formed with great ease by treating the acid chloride, anhydride, or ester, or the amide, with aniline. In the case of the negatively substituted anilines, which do not react easily with acyl anhydrides, the formation is promoted by the presence of strong acids, such as sulphuric.[1]

The anilides are colourless crystalline compounds, slightly soluble in water. Like the amides they split off the acyl group when boiled with acids or alkalies, but unlike the amides they will not do so with water alone.

The anilide and toluidide of formic acid[2] exist in two forms, one an oil easily soluble in potash, and the other a solid insoluble in potash. It is probable that these are derivatives of the two tautomeric amide formulae, the oil being $Ar{\cdot}N{=}CH{\cdot}OH$, and the solid $Ar{\cdot}NH{\cdot}CO{\cdot}H$.

The anilides form metallic derivatives which, like those of the amides, may have either of two tautomeric formulae. Thus formanilide gives with alcoholic soda a precipitate of the mono-sodium derivative, which may have the structure $H{\cdot}C\langle^{O}_{N\phi Na}$, since with methyl iodide it forms a compound which must be $H{\cdot}C\langle^{O}_{N\phi{\cdot}CH_3}$, as on hydrolysis it yields methyl aniline. Silver formanilide gives with methyl iodide an iso-(O–)-ether $H{\cdot}C\langle^{OCH_3}_{N{\cdot}\phi}$, but on the other hand with benzyl chloride it gives an N-ether $H{\cdot}C\langle^{O}_{N(\phi)CH_2{\cdot}\phi}$, which shows how untrustworthy such reactions are as proofs of constitution.

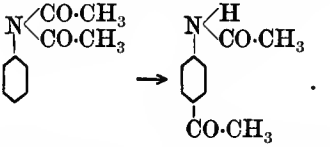
Alkyl-anilides can be made by treating the sodium-anilides with alkyl iodide; aryl-anilides, by acylating the secondary aniline bases, but this is much less easy than acylating aniline itself. For example, diphenylamine cannot like aniline be acylated by dilute formic acid, but only by concentrated: and not by acetic acid at all, but only by the acid anhydride or chloride.

The diacyl-anilines are little known. They split off one acyl with extreme ease. Thus diacetanilide $(CH_3{\cdot}CO)_2N\phi$ (obtained from acetanilide and acetic anhydride or chloride) is more than half hydrolysed into acetanilide and acetic acid by boiling for an hour with N/100 soda. If they are heated alone for some time to a rather high temperature, one of the acyl groups migrates to the ring,

[1] Smith, Orton, *J. C. S.* **1908**. 1242; **1909**. 1060.

[2] Orlow, *C.* **05**. ii. 403.

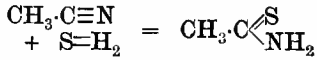
diacetanilide, for example, giving *p*-acetamino-acetophenone :—



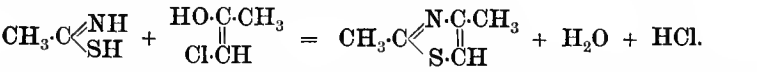
The acyl group goes mainly to the para but partly also to the ortho position.[1]

THIOAMIDES

These are amides in which the oxygen is replaced by sulphur. The simple thioamides are little known. They may be made by acting on the amides with phosphorus sulphide, or on the nitriles with hydrogen sulphide :—

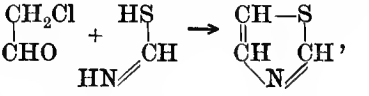


This reaction is formulated on the analogy of the amides. It is, however, more probable[2] that the thioamides have the tautomeric iso-formula $R{\cdot}C\langle^{SH}_{NH}$. This is indicated by a variety of reactions in which alkyl and other groups become attached to the sulphur. Thus with alkyl halides they often give sulphur ethers $R{\cdot}C\langle^{NH}_{SR}$. Again, with chloracetone they form thiazoles, joining up through both sulphur and nitrogen, which could scarcely happen unless both had hydrogen attached to them :—

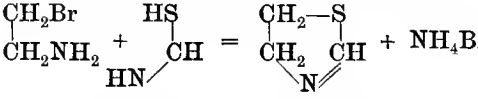


Thioformamide has recently been obtained by Willstätter and Wirth,[3] by the action of phosphorus pentasulphide on formamide. It forms colourless crystals melting at 28° to a yellow oil. It is unstable and forms an unstable salt with one molecule of hydrochloric acid. It is tautomeric, reacting according to the two formulae $H{\cdot}C\langle^{SH}_{NH}$ and $H{\cdot}C\langle^{S}_{NH_2}$. It has an acid reaction, while its di-substitution-products, such as diphenyl-thio-formamide $H{\cdot}C\langle^{S}_{N\phi_2}$, which cannot assume the imide form, have not. This suggests that the free thioformamide consists largely of the imide form. It gives a remarkably stable hydrate $H{\cdot}CS{\cdot}NH_2{\cdot}H_2O$.

Thioformamide is very reactive, and combines, for example, with chloracetaldehyde to thiazol :—



and with bromethylamine to thiazoline :—



[1] Chattaway, *Proc. C. S.* **1902.** 173 ; **1903.** 57, 124.

[2] But see Biilmann, *C.* **07.** ii. 1778.

[3] *Ber.* **42.** 1908 (1909).

It might be expected that as formamide on heating gives carbon monoxide, so thioformamide would give the unknown carbon monosulphide CS; but this is not formed, the main products of the decomposition being hydrogen sulphide and prussic acid.

The thioanilides are better known. They are most conveniently made by fusing the anilides for a short time with phosphorus pentasulphide.

Thioformanilide may also be made by the action of hydrogen sulphide on phenyl isocyanide:—

$$C{\equiv}N{\cdot}\phi + H_2S = H{\cdot}C\langle\!\!\begin{matrix}S\\NH\phi\end{matrix} \text{ or } H{\cdot}C\langle\!\!\begin{matrix}SH\\N\phi\end{matrix}.$$

Thiobenzanilide is the product of the action of phosphorus pentasulphide on benzophenone oxime, no doubt through the Beckmann reaction[1]:—

$$\phi{\cdot}\overset{\|}{C}{\cdot}\phi \rightarrow \phi{\cdot}\overset{\|}{C}{\cdot}\phi \rightarrow \phi{\cdot}\overset{\|}{C}{\cdot}SH$$
$$N{\cdot}OH \qquad N{\cdot}SH \qquad N{\cdot}\phi.$$

The thioanilides differ from the anilides in having an acid character. They form alkaline salts which are not decomposed by water, and hence dissolve in aqueous alkalies, though they are reprecipitated by carbon dioxide. This might be due to the fact that sulphur is more acidic than oxygen, as is shown by a comparison of the mercaptans with the alcohols. There seems, however, to be no doubt that the sodium salts have the metal attached to sulphur; for whenever it is removed they always join up through the sulphur. Thus the sodium salts with ethyl bromide give the thioethers $CH_3{\cdot}C\langle\!\!\begin{matrix}SEt\\N\phi\end{matrix}$. The products are proved to have this formula (1) by their being hydrolyzed by dilute acids to aniline and the esters of the thioacids:—

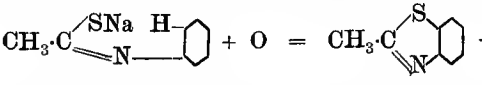
$$CH_3{\cdot}C\langle\!\!\begin{matrix}SEt\\N\phi\end{matrix} + H_2O = CH_3{\cdot}C\langle\!\!\begin{matrix}SEt\\O\end{matrix} + H_2N\phi,$$

and (2) by their giving amidines and mercaptans when treated with amines:—

$$CH_3{\cdot}C\langle\!\!\begin{matrix}SEt\\N\phi\end{matrix} + H_2N\phi = CH_3{\cdot}C\langle\!\!\begin{matrix}NH\phi\\N\phi\end{matrix} + HSEt.$$

Thus in both reactions a compound is formed in which the ethyl is attached to sulphur.

Another proof that the alkaline salts of the thioanilides have the metal attached to sulphur is that when they are oxidized with potassium ferricyanide a new ring is formed through the sulphur, giving a benzothiazol:—



We may therefore assume[2] that the salts have the formula $R{\cdot}C\langle\!\!\begin{matrix}SM\\N\phi\end{matrix}$. If the thioanilides themselves are analogous to the anilides, they must be pseudo-acids: that is, they must undergo a tautomeric change when they form salts:—

$$R{\cdot}C\langle\!\!\begin{matrix}S\\NH\phi\end{matrix} \rightarrow R{\cdot}C\langle\!\!\begin{matrix}SM\\N\phi\end{matrix}.$$

[1] Ciusa, *C.* **07.** i. 28.

[2] The evidence, however, is not conclusive. See Biilmann, *Ann.* **364.** 314 (1909).

That this is so is quite possible, especially in view of the fact that they react with hydroxylamine to give anilido-oximes:—

$$CH_3{\cdot}C\langle\begin{matrix}S\\NH\phi\end{matrix} + H_2NOH = CH_3{\cdot}C\langle\begin{matrix}NOH\\NH\phi\end{matrix} + H_2S.$$

IMIDES

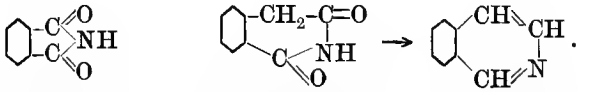
The imides are the cyclic secondary amides of the dibasic acids:—

$$R\langle\begin{matrix}CO{\cdot}OH\\CO{\cdot}OH\end{matrix} + H_3N \rightarrow R\langle\begin{matrix}C{=}O\\C{=}O\end{matrix}\rangle NH.$$

Their formation is practically confined to those acids in which the two carboxyls are separated by a chain of 2 or 3 carbon atoms; that is, where the imide contains a 5- or a 6-ring. This is analogous to the formation of the cyclic anhydrides, which, however, are also produced by acids with still longer chains, which do not give imides. It is an example of the truth of Baeyer's strain theory, that the rings most easily formed are those containing 5 atoms, and next those of 6.

An imide of oxalic acid $\begin{matrix}CO\\|\\CO\end{matrix}\rangle NH$ has been described,[1] but its existence is doubtful, and its structure still more so. Malonic acid gives no imide, nor do adipic and the higher members of the series; but succinic and glutaric acids form them with great ease.

Among the phthalic acids it is only the ortho which gives an imide. Iso-(meta)-phthalic acid, though it has like glutaric acid three carbon atoms between the carboxyls, gives neither an imide nor an anhydride, evidently because the rigid structure of the benzene ring holds the carboxyls further apart than in an open-chain compound. This view is confirmed by the fact that homophthalic acid, which like isophthalic acid has three carbons between the carboxyls, but has one of these in a side chain, forms both an imide and an anhydride. The structure of this imide is established by its conversion, on treatment with phosphorus oxychloride and subsequent reduction, into isoquinoline:—



Phthalimide Homophthalimide Isoquinoline

The imides in general are formed by heating the ammonium salts, the diamides, or the monamides (-amic acids) of dibasic acids:—

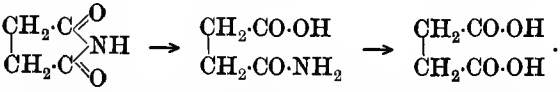
$$\begin{matrix}CH_2{-}C\langle\begin{matrix}O\\NH_2\end{matrix}\\|\\CH_2{-}C\langle\begin{matrix}NH_2\\O\end{matrix}\end{matrix} = NH_3 + \begin{matrix}CH_2{-}C\langle\begin{matrix}O\\NH\end{matrix}\\|\\CH_2{-}C\langle\begin{matrix}\\O\end{matrix}\end{matrix},$$

or most conveniently by heating the anhydrides in a stream of ammonia.

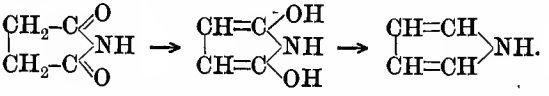
[1] Ost, Mente, *Ber.* **19.** 3228 (1886).

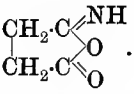
They may also be got by the partial hydration of the dicyanides,[1] such as ethylene dicyanide.

They are easily hydrolysed by alkalies to give first the -amic acid, and then the acid itself:—

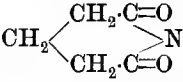


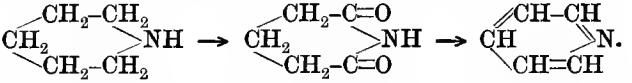
On reduction succinimide is converted into pyrrol derivatives; thus on distillation over zinc dust it gives pyrrol itself, a reaction which is most clearly represented as taking place through the tautomeric dienolic form:—



This reaction proves that succinimide has the symmetrical formula given above, and not the possible unsymmetrical structure  .

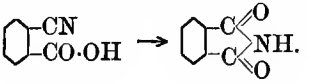
The combined influences of the two carbonyl groups and of the ring structure render the imide hydrogen distinctly acidic; and succinimide forms a potassium salt even with alcoholic potash. A silver salt is also known, whose electrical behaviour is peculiar.[2] The concentration of silver ion in its aqueous solution, as measured by the E. M. F., is only half that required by the conductivity. This indicates that it breaks up to give some other cations than silver.

Glutarimide  resembles succinimide. It can be obtained[3] by the oxidation of piperidine with hydrogen peroxide, and on distillation over zinc dust it gives a small quantity of pyridine:—



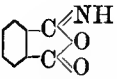
Piperidine Glutarimide Pyridine

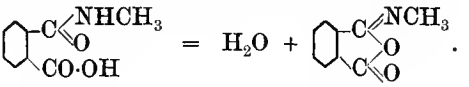
Phthalimide, the imide of ortho-phthalic acid, is a body of great practical importance, both for Gabriel's synthesis of amines, which has already been so frequently mentioned, and also as an intermediate compound in the commercial preparation of indigo. It can be made by acting with ammonia on phthalic anhydride, and is also formed[4] by a curious intramolecular change when *o*-cyan-benzoic acid is heated to its melting-point (180–190°):—



[1] Bogert, Eccles, *J. Am. Ch. Soc.* **24**. 20 (*C.* **02**. i. 711).
[2] Ley, Schäfer, *Ber.* **39**. 1259 (1906).
[3] Wolffenstein, *Ber.* **25**. 2777 (1891).
[4] Hoogewerff, van Dorp, *Rec. Trav.* **11**. 84 (1892).

Its imide hydrogen is sufficiently acidic for it to dissolve in aqueous potash. If the potassium salt is treated with alkyl iodide, a symmetrical alkyl phthalimide  is produced.

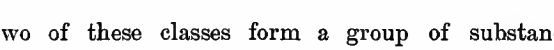
Although no unsymmetrical isomeric phthalimide  is known, its alkyl derivatives can be obtained by treating the alkyl-phthalamic acids with acetic anhydride, which acts merely as a dehydrating agent [1]:—



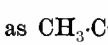
AMIDO-CHLORIDES. IMIDO-CHLORIDES. IMIDO-ETHERS

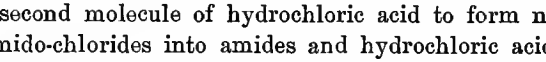
The last two of these classes form a group of substances which are derived from the iso-amides, having the NH group attached to carbon by a double bond.

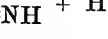
The *amido-chlorides* themselves are derived from the normal amides, and are obtained by acting on them with phosphorus pentachloride:—

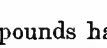


the action being analogous to that of phosphorus pentachloride on aldehydes and ketones.

The amido-chlorides lose hydrochloric acid with the greatest ease to form imido-chlorides, such as  . These bodies are rather more stable, but they readily lose a second molecule of hydrochloric acid to form nitriles. Water converts the imido-chlorides into amides and hydrochloric acid:—



The *imido-chlorides* are really the acid chlorides of the imido-acids or iso-amides  , which, however, seem to be incapable of existence, and to pass over as soon as they are formed into the more stable amides.

In the case of the α-oxy-acids, such as glycollic acid, it was formerly supposed that the true imido-acids could be isolated. Glycollic acid gives a normal amide $CH_2OH{\cdot}CO{\cdot}NH_2$; but if its anhydride is treated with ammonia, or if its imido-ether is saponified, an isomeric substance is obtained,[2] which was originally assumed to be the iso-amide or imidohydrine  . Analogous compounds have been obtained from other α-oxy-acids. The subject has been reinvestigated by Hantzsch and Voegelen,[3] who have shown that the properties of these substances are incompatible with this structure—and, indeed, as far as one can see, with any structure. They cannot be converted

[1] Hoogewerff, van Dorp, *Rec. Trav.* **13**. 93 (1894).
[2] Eschweiler, *Ber.* **30**. 998 (1897). [3] *Ber.* **34**. 3142 (1901).

into the amides, a change which one would expect to occur with the utmost ease, and their molecular weight is twice that required by the simple formula. Their other properties are also most extraordinary. Though they are only weak bases, and are not acidic at all, their solutions are very good conductors of electricity, so that their electrolytic behaviour is that of salts. Moreover, though they are fairly stable to acids, they are easily decomposed by certain salts, such as calcium chloride, with the formation of a glycollate. No satisfactory hypothesis has yet been proposed to account for these phenomena.

The esters of the imido-acids, the *imido-ethers,* are much better known than the acids themselves or their chlorides. The hydrochlorides of these imido-ethers are formed by passing hydrochloric acid into a mixture of a nitrile and an alcohol in molecular proportions, diluted with ether and well cooled. The hydrochloride of a chlor-amido-ether is first produced:—

$$CH_3{\cdot}C{\equiv}N + C_2H_5OH + 2\,HCl = CH_3{\cdot}C\begin{cases}NH_2{\cdot}HCl\\OC_2H_5\\Cl\end{cases}.$$

This is very unstable, and loses hydrochloric acid to form the hydrochloride of an imido-ether $CH_3{\cdot}C\begin{cases}NH{\cdot}HCl\\OC_2H_5\end{cases}$. The chlor-amido-ethers[1] are much more stable if the two hydrogens of the amino-group are replaced by two alkyls: though even then they are decomposed by heat, giving first the imido-chloride and one molecule of alkyl chloride, and then the nitrile and two molecules of alkyl chloride:—

$$R{\cdot}C\begin{cases}NEt_2{\cdot}HCl\\OC_2H_5\\Cl\end{cases} = R{\cdot}C\begin{cases}NEt{\cdot}HCl\\OC_2H_5\end{cases} + EtCl = R{\cdot}C{\equiv}N + 2\,EtCl + EtOH.$$

The hydrochlorides of the imido-ethers are crystalline bodies which on heating lose alkyl chloride and form amides:—

$$CH_3{\cdot}C\begin{cases}NH{\cdot}HCl\\OC_2H_5\end{cases} = CH_3{\cdot}C\begin{cases}NH_2\\O\end{cases} + C_2H_5Cl.$$

If treated with soda under ether they give the free imido-ethers, such as $CH_3{\cdot}C\begin{cases}NH\\OC_2H_5\end{cases}$, a liquid boiling at 97°.

The imido-ethers present a remarkable case of intramolecular rearrangement. A variety of substituted imido-ethers are known, in which the imide hydrogen is replaced by hydrocarbon radicals. They may be made from the simple ethers by alkylation; or by starting with an alkyl (or aryl) amide, converting this into the imido-chloride, and treating this with sodium alkylate:—

$$CH_3{\cdot}C\begin{cases}NH\phi\\O\end{cases} \longrightarrow CH_3{\cdot}C\begin{cases}N\phi\\Cl\end{cases} \xrightarrow{NaOEt} CH_3{\cdot}C\begin{cases}N\phi\\OC_2H_5\end{cases}.$$

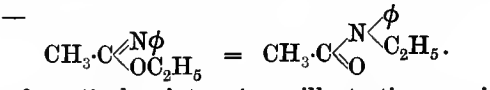
Now the imido-ethers behave on heating[2] in different ways according as the imide hydrogen is substituted or not. The simple ethers, where it is not substituted, break up back again into nitrile and alcohol:—

$$CH_3{\cdot}C\begin{cases}NH\\OC_2H_5\end{cases} = CH_3{\cdot}C{\equiv}N + C_2H_5OH.$$

[1] v. Braun, *Ber.* **37**. 2678, 2812 (1904).

[2] W. Wislicenus, *Ber.* **35**. 164 (1902).

If the imide hydrogen is replaced this reaction does not occur; but instead of this, at about 200°, a rearrangement takes place, and a di-substituted amide is formed:—

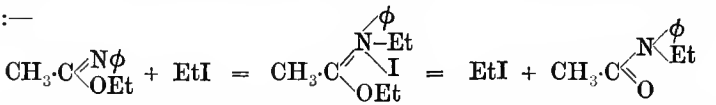


This reaction is of particular interest as illustrating an intermediate stage between an ordinary (isomeric) and a true tautomeric change. The imido-acids (iso-amides) go over spontaneously into the normal amides:—

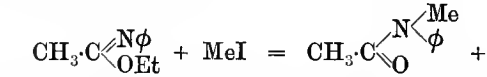


This is what is known as a tautomeric change, occurring spontaneously, and consisting only in the passage of a hydrogen atom from one position to another; it is supposed to be due to the great 'mobility' of the hydrogen. It appears, however, that if the hydrogen atom is replaced by an alkyl group, this can 'wander' also, only not so easily. Instead of changing at the ordinary temperature the substance requires to be heated to about 200°. Accordingly, we find, as we should expect, that a methyl group wanders more easily than an ethyl, though the difference is not very great.[1] It is evident that the distinction between such a reaction as this and a true tautomeric change is one of degree and not of kind, and that the phenomenon of tautomerism is not confined to the case of the 'wandering' hydrogen atom, although it occurs in that case with peculiar ease.

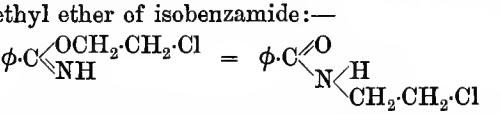
The conversion of the imido-ethers into the substituted amides can be brought about much more easily in the presence of an alkyl halide, such as ethyl iodide. It then takes place slowly at the ordinary temperature, and rapidly at 100°. But here it can be shown that an intermediate compound is formed:—



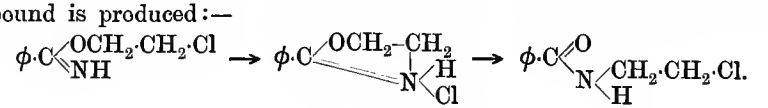
This is probable because, if the iodide of a different alkyl is used, an exchange of alkyl groups sometimes occurs:—



It is further shown by the following facts. There is one case of an imido-ether which changes into the amide below 100° without the addition of alkyl iodide. This is the chlorethyl ether of isobenzamide:—



This is the solitary case where the addition of an alkyl halide is not required, and the reason obviously is that the chlorethyl group is able to attach itself to the nitrogen in exactly the same way as an alkyl halide, save that a ring compound is produced:—



Lander, *J. C. S.* **1903**. 406.

If the original body is heated on a water bath it first melts, then solidifies, and then melts again. If the solid, before it can melt again, is dissolved in water and treated with silver nitrate, it gives a precipitate of silver chloride, which it does not do before or after this point, showing that the hydrochloride of the base is formed. Indeed, if the intermediate solid phase is rapidly cooled, the ring compound can actually be isolated from it.

If the hydrochlorides of the imido-ethers are treated with excess of alcohol, they first dissolve and then precipitate ammonium chloride, with the formation of an ortho-ester of the original acid:—

$$R{\cdot}C\begin{matrix}\diagup NH{\cdot}HCl\\ \diagdown OC_2H_5\end{matrix} + \begin{matrix}HO{\cdot}C_2H_5\\ HO{\cdot}C_2H_5\end{matrix} = R{\cdot}C\begin{matrix}\diagup OEt\\ -OEt\\ \diagdown OEt\end{matrix} + NH_4Cl.$$

With alcoholic ammonia, the imido-ethers react like an ordinary ester. The ethoxy group is replaced by NH_2, and an amidine is produced:—

$$R{\cdot}C\begin{matrix}\diagup NH\\ \diagdown OC_2H_5\end{matrix} + NH_3 = R{\cdot}C\begin{matrix}\diagup NH\\ \diagdown NH_2\end{matrix} + HO{\cdot}C_2H_5.$$

The amidines can also be made by heating the amides in a stream of hydrochloric acid gas:—

$$\begin{matrix}CH_3{\cdot}C\begin{matrix}\diagup NH_2\\ \diagdown O\end{matrix}\\ + \ CH_3{\cdot}C\begin{matrix}\diagup O\\ \diagdown NH_2\end{matrix}\end{matrix} = \begin{matrix}CH_3{\cdot}C\begin{matrix}\diagup OH\\ \diagdown O\end{matrix}\\ + \ CH_3{\cdot}C\begin{matrix}\diagup NH\\ \diagdown NH_2\end{matrix}\end{matrix},$$

or by heating the nitriles with ammonium chloride:—

$$\begin{matrix}CH_3{\cdot}C{\equiv}N\\ + \quad H_2N{\cdot}H\end{matrix} = CH_3{\cdot}C\begin{matrix}\diagup NH\\ \diagdown NH_2\end{matrix}.$$

They are at once amides and imides of the acid. They are strong monacid bases, giving stable salts. The free amidines have an alkaline reaction, and are easily hydrolysed into the acid and ammonia.

CHAPTER V

HYDROXYLAMINE DERIVATIVES

THESE fall into three classes:—

A. Those in which one or more of the hydrogen atoms in hydroxylamine are replaced by as many organic radicals: these are what are generally meant by the hydroxylamine derivatives.

B. Derivatives of the hypothetical tautomer of hydroxylamine $H_3N{=}O$: the amine-oxides.

C. Derivatives of hydroxylamine in which the two hydrogen atoms attached to the nitrogen are replaced by a divalent radical, the oximes or isonitroso-compounds $\begin{matrix}R\\R_1\end{matrix}\!\!>\!C{=}NOH$.

The third group is by far the most numerous and important, but the first two also contain some interesting compounds.

TRUE HYDROXYLAMINE DERIVATIVES

The mono-derivatives are of two kinds, according as the hydrogen replaced is attached to nitrogen or oxygen. Those in which it is attached to oxygen, of the type $H_2N{\cdot}O{\cdot}R$, are known as α-hydroxylamine compounds, those in which it is on the nitrogen as β.

The α-hydroxylamines (O-ethers) are obtained from the oximes. If an oxime is boiled with acids it goes back into hydroxylamine and the aldehyde or ketone from which it was formed. If the oxime is treated with alkyl iodide and sodium ethylate it is converted into its alkyl (O-) ether:—

$$\phi{\cdot}CH{=}NOH + C_2H_5I = HI + \phi{\cdot}CH{=}NOC_2H_5,$$

and when this ether is boiled with acids it splits in the same way as the oxime itself, giving the O-ether of hydroxylamine:—

$$\phi{\cdot}CH{=}NOC_2H_5 + H_2O = \phi{\cdot}CHO + H_2NOC_2H_5.$$

That the product, ethyl-α-hydroxylamine, is really an O-ether is shown by its splitting off ethyl chloride with hydrochloric acid at 150°, which would not occur if the ethyl was attached to nitrogen.

The β-hydroxylamines or N-ethers are got by the partial reduction of the nitro-compounds. Thus nitromethane is converted by reduction with zinc dust and water into β-methyl-hydroxylamine:—

$$CH_3{\cdot}N\begin{matrix}\nearrow O\\ \searrow O\end{matrix} + 2\,H_2 = CH_3{\cdot}N\begin{matrix}\diagup H\\ \diagdown OH\end{matrix} + H_2O,$$

a reaction which proves the structure of the latter. The reduction may also be effected by ammonium sulphide.[1]

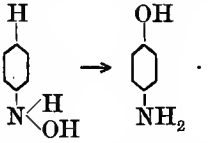
β-phenyl hydroxylamine, $\phi{\cdot}NHOH$, is of interest because of the remarkable

[1] Willstätter, Kubli, *Ber.* **41**. 1936 (1908).

changes which it can undergo. For a long time all attempts to prepare it were unsuccessful, the product obtained being, most unexpectedly, *p*-aminophenol. Thus one would expect it to be formed by boiling phenyl azide, $\phi \cdot N_3$, with dilute acids, according to the equation

$$\phi \cdot N\langle \begin{matrix} N \\ \| \\ N \end{matrix} + \begin{matrix} H \\ | \\ OH \end{matrix} = \phi \cdot N\langle \begin{matrix} H \\ OH \end{matrix} + N_2;$$

but *p*-aminophenol is produced instead, as it is also in the electrolytic reduction of nitrobenzene. These facts show that *β*-phenyl-hydroxylamine must be an unstable body, readily changing into *p*-aminophenol:—



This view has been fully confirmed by the work of Bamberger, who has succeeded in preparing *β*-phenyl-hydroxylamine in various ways, and has investigated its properties in great detail.

In order to prepare it, nitrobenzene is covered with water or dissolved in hot alcohol, and reduced with zinc dust, the reduction being promoted by the presence of neutral salts such as calcium or ammonium chloride:—

$$\phi \cdot N\langle \begin{matrix} O \\ O \end{matrix} + 2\,H_2 = \phi \cdot N\langle \begin{matrix} H \\ OH \end{matrix} + H_2O.$$

The solution must be neutral or aminophenol is formed; this is why the earlier attempts to prepare the body failed. The reaction is exactly parallel to V. Meyer's preparation of the fatty *β*-hydroxylamines by reduction of the nitroparaffins. By this method of reduction with zinc dust in neutral solution in the presence of a salt, any nitro-compound can be converted into a *β*-hydroxylamine.

They can also be obtained[1] by the electrolytic reduction of the nitro-compounds in the presence of acetic acid, the concentration of hydrogen ion being kept low by the addition of sodium acetate.

Further, the *β*-hydroxylamines are, as Bamberger has shown, the first products which can be isolated of the oxidation of primary or secondary amines with potassium permanganate, hydrogen peroxide, Caro's acid (sulpho-mono-peracid, $\begin{matrix} HO \cdot O \\ HO \end{matrix}\rangle SO_2$, obtained by dissolving a persulphate in sulphuric acid), and other substances. The final products of such oxidations are very numerous and complicated, but they are all such as would be obtained from the hydroxylamines, which can be isolated in many cases. It is probable that the actual first oxidation product in the case of the primary and secondary amines is, as it certainly is in that of the tertiary, the amine-oxide $Ar \cdot NH_2 : O$ or $Ar_2 \cdot NH : O$, and that this then changes into the tautomeric *b*-hydroxylamine, e.g.

$$\begin{matrix} \phi \\ H\text{–}N \\ H \end{matrix}\rangle + O = \begin{matrix} \phi \\ H\text{–}N{=}O \\ H \end{matrix}\rangle \longrightarrow \begin{matrix} \phi \\ H \end{matrix}\rangle N \cdot OH.$$

[1] Brand, *Ber.* **38**. 3076 (1905).

β-phenyl-hydroxylamine $\phi\cdot NH\cdot OH$ is a colourless crystalline substance melting at 81°. It reduces ammoniacal silver solutions and Fehling's solution in the cold. It is an unstable body in solution, and breaks up in a variety of ways. In alkaline solution in the absence of air one part oxidizes another, giving nitrosobenzene and aniline:—

$$2\,\phi\cdot NHOH = \phi\cdot NO + \phi\cdot NH_2 + H_2O.$$

The nitrosobenzene so formed reacts with unchanged phenyl-hydroxylamine to give azoxybenzene:—

$$\phi\cdot NO + \begin{matrix}HO\\H\end{matrix}\!\!>\!N\cdot\phi = \phi\cdot\overset{\displaystyle O}{\overset{\diagup\diagdown}{N}}\!-\!N\cdot\phi + H_2O.$$

If the air is not excluded, the solution rapidly absorbs oxygen. If the (neutral) aqueous solution is exposed to the air, the body is oxidized to nitrosobenzene, which combines as before with unchanged hydroxylamine to form azoxybenzene. At the same time, for each molecule of nitrosobenzene formed, one molecule of hydrogen peroxide is produced. That is to say, in this, as in other 'autoxidations', for whatever reason, one half of the oxygen goes to the substance oxidized, and the other half combines with the water.

The alkaline solution[1] is much more easily oxidized by the air, so easily that it can be used like pyrogallate for removing oxygen in gasometry.[2] In this case only traces of hydrogen peroxide can be detected, while much nitrobenzene is formed, the hydrogen peroxide being used up in presence of the alkali to oxidize nitrosobenzene, the primary product, to nitrobenzene.

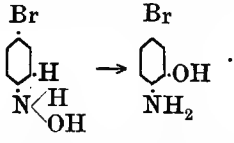
With aldehydes, the β-hydroxylamines form the N-ethers of the oximes:—

$$Ar\cdot N\!<\!\begin{matrix}H\\OH\end{matrix} + O{=}CH\cdot\phi = Ar\cdot\overset{\displaystyle O}{\overset{\diagup\diagdown}{N}}\!-\!CH\cdot\phi + H_2O.$$

(Compare the strictly analogous reaction with nitrosobenzene, giving oxyazobenzene.)

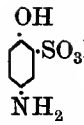
When warmed with acids, they undergo the remarkable change already mentioned into aminophenols. Bamberger[3] has investigated this change in great detail, with a variety of hydroxylamines, and finds that the following rules hold good.

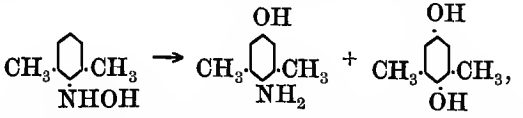
Aryl hydroxylamines with the para position open are converted by sulphuric acid (or by alum solution) into para-aminophenols; while, if there is a halogen in the para position, an ortho-aminophenol is formed:—



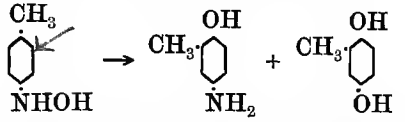
Sometimes these ortho-derivatives are produced even when the para position is not occupied. In many cases, if sulphuric acid is used, a *p*-aminophenol

[1] Bamberger, *Ber.* **33.** 113 (1900).
[2] Bamberger, Brady, *Ber.* **33.** 271.
[3] *Ber.* **33.** 3600 (1900).

sulphonic acid, as  , is obtained. If alcoholic sulphuric acid is used, the *p*- and *o*-phenol ethers are obtained, although they are not formed by treating the aminophenols with alcohol and sulphuric acid. In some cases the formation of *p*-aminophenols is accompanied by that of the corresponding hydroquinones, e. g.:—



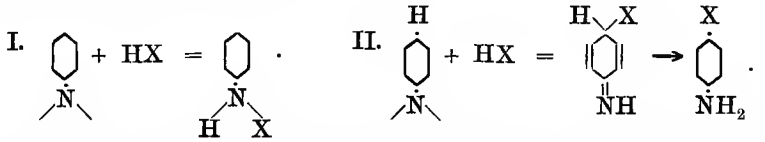
and sometimes, too, if there is a para methyl group in the original hydroxylamine, this is moved on to the next carbon atom:—



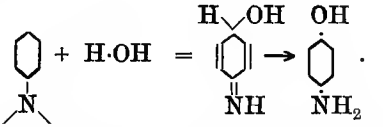
The possibility that these hydroquinones are formed by the hydrolysis of the aminophenols is excluded by direct experiment, which shows that this hydrolysis does not occur.

These remarkable changes—and there are others which have not been mentioned—Bamberger proposes to explain by the following hypothesis,[1] which, though it cannot be regarded as established, is sufficiently ingenious to be worth considering.

He supposes that the first action of the sulphuric acid solution on the hydroxylamine is to remove water, giving the residue Ar·N<, which is unstable, and immediately reacts with the other substance, HX, which is present, adding on H and X in one of two ways:—



In the case we have been dealing with, of the action of dilute acid, the body added on is generally water. This goes according to the first equation, giving first an imino-quinole:—

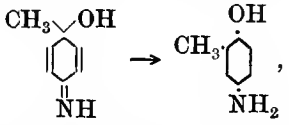


These imino-quinoles, with hydrogen still attached to the para carbon atom, are unstable, and immediately change over to the aminophenols, and thus we get the normal reaction, leading to the para-aminophenols.

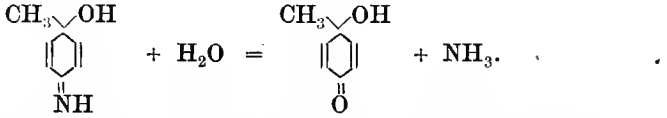
If the para hydrogen is replaced by methyl, the imino-quinoles are more

[1] *Ber.* **34.** 61 (1901). Cf. *Ber.* **40.** 1893 (1907).

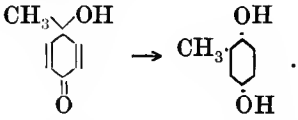
stable. They can then only change into aminophenols by the migration of the methyl group,



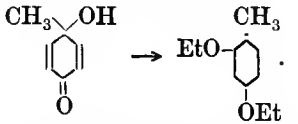
and to a small extent this takes place. But the greater part undergoes a different decomposition; the NH is split off, and quinoles are formed. These can actually be isolated, and are indeed the main products of the reaction.



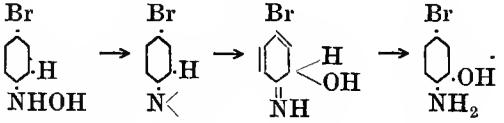
They are, however, capable of further change, the quinoid ring having a strong tendency to go back to the normal aromatic structure. This can only happen by the migration of one of the two groups, hydroxyl and methyl, attached to the para carbon. Both of these groups can migrate. The methyl does so to a certain extent in the course of the reaction in which the quinoles are formed, with the production of a hydroquinone:—



On the other hand, in the presence of alcoholic sulphuric acid, the hydroxyl migrates, being etherified at the same time:—



The formation of ortho-aminophenols can be explained in the same way, except that the derivative of an ortho-quinone is produced:—



All these are examples of the second of the two possible reactions of the unsaturated group Ar·N<. There are also cases of the first reaction. For instance, phenyl hydroxylamine reacts with aniline to give *o*- and *p*-amino-diphenylamine:—

$$\phi\cdot N< + H\cdot C_6H_4\cdot NH_2 = \phi\cdot N<^{H}_{C_6H_4\cdot NH_2}.$$

Again, tolyl hydroxylamine and phenol form *p*-oxy-phenyl-*p*-tolyl-amine:—

$$CH_3\cdot C_6H_4N + H\cdot C_6H_4\cdot OH = CH_3\cdot C_6H_4\cdot N<^{H}_{C_6H_4\cdot OH}.$$

The β-β-dialkyl-hydroxylamines $(Alk)_2NOH$ can be made by the oxidation of the secondary amines,[1] and similar compounds are got from the cyclic secondary amines, e. g. $C_5H_{10}N{\cdot}OH$ from piperidine and hydrogen peroxide.[2] They are also formed in two singular reactions, by treating zinc alkyl or magnesium alkyl halide with an alkyl nitrite or a nitroparaffin.[3] With an alkyl nitrite a substituted hydroxylamine is obtained which has the two alkyls from the zinc alkyl; and we may assume an intermediate product to be formed which is then broken up by water:—

$$C_5H_{11}{\cdot}O{\cdot}N{=}O + 2\,Zn(CH_3)_2 \rightarrow \begin{matrix} C_5H_{11}{\cdot}O \\ CH_3{\cdot}Zn \end{matrix}\!\!>\!N{-}\begin{matrix} O{\cdot}ZnCH_3 \\ CH_3 \\ CH_3 \end{matrix} \rightarrow C_5H_{11}{\cdot}OH + N{-}\begin{matrix} OH \\ CH_3 \\ CH_3 \end{matrix}.$$

With a nitroparaffin one of the alkyl groups is added on to the carbon chain, apparently through the tautomeric isonitro form:—

$$CH_3{\cdot}CH_2{\cdot}NO_2 \rightarrow CH_3{\cdot}CH{=}N\begin{matrix} O \\ OH \end{matrix} \rightarrow \begin{matrix} CH_3{\cdot}CH{\cdot}N \\ | \\ CH_3{\cdot}CH_2 \end{matrix}\!\!<\!\begin{matrix} OH \\ CH_2{\cdot}CH_3 \end{matrix}.$$

This last substance was for some time supposed to be triethylamine oxide $(C_2H_5)_3N{=}O$.

AMINE-OXIDES OR OXY-AMINES

These bodies are derivatives of the hypothetical tautomeric form of hydroxylamine $H_3N{=}O$.

The first compounds of this type were prepared by Dunstan and Goulding,[4] by the action of methyl iodide on hydroxylamine. The product is the hydriodide of trimethylamine oxide, $(CH_3)_3N\!<\!\begin{matrix} OH \\ I \end{matrix}$, which, when treated with potash, gives the oxide $(CH_3)_3N{=}O$. If ethyl iodide is used instead of methyl iodide, the true hydroxylamine derivative $Et_2N{\cdot}OH$ is formed first, and this on further treatment with ethyl iodide takes up another ethyl group, giving $Et_3N{=}O$. With propyl or isopropyl iodide the action stops at the first stage, with the production of $Pr_2N{\cdot}OH$.

A simpler method of preparation, also due to Dunstan, is to treat the tertiary amines with hydrogen peroxide, when they are directly oxidized to the amine-oxide:— $Pr_3N + O = Pr_3N{=}O$.

These oxy-amines have not been obtained in the anhydrous state. They separate from water in the form of hygroscopic crystals of a hydrate, e. g. $(CH_3)_3N{=}O,\ 2\,H_2O$, which retains its water of crystallization with great firmness. The solution has a strong alkaline reaction, and it does not reduce Fehling's solution, showing that the body is not a true hydroxylamine derivative. When treated with acid it gives a salt such as $(CH_3)_3N\!<\!\begin{matrix} OH \\ I \end{matrix}$, so that it behaves as if one of the molecules of water was chemically united

[1] Mamlock, Wolffenstein, *Ber.* **33.** 159 (1900); **34.** 2499 (1901).
[2] Wolffenstein, Haase, *Ber.* **37.** 3228 (1904).
[3] Bewad, *J. pr. Ch.* [2] **63.** 94, 193 (1901); *Ber.* **40.** 3065 (1907).
[4] *J. C. S.* **1899.** 792, 1004.

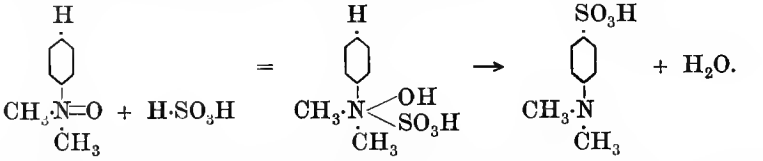
to form a dihydroxy-compound $(CH_3)_3N\langle^{OH}_{OH}$. Similarly, it combines with methyl iodide to give the ether-salt $(CH_3)_3N\langle^{OCH_3}_{I}$.

When it is heated, trimethylamine-oxide breaks up with the loss of a methyl group into dimethylamine and formaldehyde :—

$$(CH_3)_3N{=}O \;=\; (CH_3)_2NH \;+\; CH_2O.$$

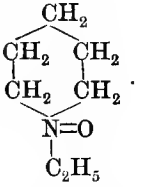
When reduced with zinc dust it gives trimethylamine, which is a proof that all three methyl groups are directly attached to nitrogen.

An analogous series of compounds are the oxides of the aromatic amines, prepared by Bamberger,[1] by direct oxidation. They are formed almost quantitatively from any tertiary mixed amines, such as dimethyl-aniline, dimethyl-toluidine, &c., by treatment with hydrogen peroxide or Caro's acid.[2] They are crystalline compounds ($\phi N(CH_3)_2{=}O$ melts at 152°) which are excessively hygroscopic, but apparently do not form definite hydrates. When heated above their melting-points they break up mainly into tertiary base and oxygen. They have an alkaline reaction and form salts with acids. They resemble Dunstan's alkyl compounds in their general behaviour, with one important exception. Owing to the presence of the benzene ring they can form substitution-products, and do so with great ease. Thus they give sulphonic acids with sulphurous acid and nitro-derivatives with nitrous acid. We may assume that in these cases the salts are first produced, and then isomerize :—



The positions taken up by the substituents are ortho and para. In the case of the sulphonic acid it is mainly the ortho that is formed; in the nitro-compound about equal quantities of the two are obtained. The reaction is parallel to the ordinary substitution of aniline; but it is to be noticed that the nitrogen is here pentavalent, which, however, seems to make no difference to the result.

A third group of similar compounds has been prepared by Haase and Wolffenstein by the action of hydrogen peroxide on the alkyl-piperidines :[3] e. g. from N-ethyl-piperidine the oxide



[1] *Ber.* **32**. 342, 1882 (1899); **34**. 12 (1901); **35**. 1082 (1902).

[2] Similar compounds can be prepared from the leuco-bases of the triphenyl methane dyes, such as malachite green and crystal violet. Bamberger, Rudolf, *Ber.* **41**. 3290 (1908).

[3] *Ber.* **31**. 1553 (1898); **32**. 2507 (1899).

Unlike the fatty, but like the aromatic derivatives, these bodies lose oxygen when distilled, re-forming the alkyl-piperidine. Indeed, the oxygen appears to be much more loosely attached than in either of the other two series; thus they break up into alkyl-piperidine and oxygen with almost explosive violence if heated in a current of hydrochloric acid, and they liberate iodine from potassium iodide on warming.

As has already been mentioned, methyl-ethyl-aniline oxide, $\phi(CH_3)(C_2H_5)N{=}O$, can be broken up by the fractional crystallization of its *d*-brom-camphor sulphonate, into two optically active forms, which retain their activity not only when converted into the chlorides, but also in solution when treated with baryta, i. e. in the form of the oxide or hydroxide.[1]

HYDROXAMIC ACIDS

These bodies are related to the amides as hydroxylamine to ammonia, and like the amides they have two possible formulae:—

$$R{\cdot}C\langle^{O}_{NH{\cdot}OH} \quad \text{and} \quad R{\cdot}C\langle^{OH}_{NOH}.$$

In no instance have the two tautomers been separated, and it is even more difficult here than in the case of the amides to decide which of the two represents the actual structure; there are arguments of no great weight on either side.

The hydroxamic acids are formed (like the amides) by the action of hydroxylamine on the esters or on the acid anhydrides.[2] In the latter case an acyl-hydroxamic acid (generally known as a di-hydroxamic acid) is produced, which is easily hydrolysed by alkalies to form the hydroxamic acid:—

$$\begin{matrix}CH_3{\cdot}C\langle^{O}\\CH_3{\cdot}C\langle^{O}\end{matrix} + H_2NOH = CH_3{\cdot}C\langle^{O}_{NH{\cdot}O{\cdot}CO{\cdot}CH_3} \rightarrow CH_3{\cdot}C\langle^{O}_{NH{\cdot}OH}.$$

They are also formed (often even in the cold) by the action of hydroxylamine on the amides, ammonia being expelled.

They can further be obtained[3] by oxidizing the aldoximes with Caro's acid:—

$$R{\cdot}C\langle^{H}_{NOH} \rightarrow R{\cdot}C\langle^{OH}_{NOH},$$

which resembles the oxidation of an aldehyde to an acid. Since the aldoximes are themselves formed by the oxidation of amines of the type $R{\cdot}CH_2{\cdot}NH_2$ with Caro's acid, the hydroxamic acids are among the products of oxidation of such amines.[4] They are also formed from the nitroparaffins by intramolecular change: for example, in small quantity by acidifying their alkaline solution[5]:—

$$R{\cdot}CH{=}N\langle^{O}_{OH} \rightarrow R{\cdot}C\langle^{OH}_{NOH}$$

—a somewhat unusual migration of oxygen. In the same way the sodium

[1] Meisenheimer, *Ber.* **41**. 3966 (1908). See above, p. 30.
[2] Jeanrenaud, *Ber.* **22**. 1270 (1889). Cf. Morelli, *C.* **08**. ii. 1019.
[3] Bamberger, *Ber.* **34**. 2029 (1901). [4] Bamberger, *Ber.* **36**. 710 (1903).
[5] Bamberger, Rüst, *Ber.* **35**. 45 (1902).

salts of the nitroparaffins when treated with acyl chloride form the di-hydroxamic acids[1]:—

$$CH_3{\cdot}CH{=}N\langle^{O}_{ONa} \rightarrow CH_3{\cdot}CH{=}N\langle^{O}_{O{\cdot}CO{\cdot}R} \rightarrow CH_3{\cdot}C\langle^{OH}_{N{\cdot}O{\cdot}CO{\cdot}R}.$$

The hydroxamic acid chlorides (having of course the hydroxyl on the carbon replaced by chlorine) can be got by the action of hydrochloric acid on the alkyl-nitrolic acids[2]:—

$$CH_3{\cdot}C\langle^{NO_2}_{NOH} + HCl = CH_3{\cdot}C\langle^{Cl}_{NOH} + HNO_2,$$

or by the action of chlorine on the aldoximes[3]:—

$$CH_3{\cdot}C\langle^{H}_{NOH} \rightarrow CH_3{\cdot}C\langle^{Cl}_{NOH}.$$

The alkyl-hydroxamic acids are neutral, while the aromatic have an acid reaction. They all, however, form salts, the ferric salts having a characteristic deep red colour. Form hydroxamic acid, $H{\cdot}C\langle^{OH}_{NOH}$ (obtained, for example, from formic ester and hydroxylamine), melts at 81–82°, and explodes above this temperature, decomposing into carbon monoxide and hydroxylamine. Its chloride, $H{\cdot}C\langle^{Cl}_{NOH}$, also known as formyl chloride oxime, is closely related to fulminic acid, from which it can be obtained by the action of hydrochloric acid, and into which it is very easily converted:—

$$H{\cdot}C\langle^{Cl}_{NOH} \rightleftharpoons HCl + C{=}N{\cdot}OH.$$

Di-acet-hydroxamic acid, $CH_3{\cdot}C\langle^{OH}_{NO{\cdot}CO{\cdot}CH_3}$, obtained from hydroxylamine hydrochloride and acetic anhydride, is a strong acid, readily hydrolysed by excess of alkali to acet-hydroxamic acid. But if it is treated with half a molecular proportion of potassium carbonate it gives symmetrical dimethyl urea. This change probably takes place (like the Hofmann reaction) through the Beckmann rearrangement:—

$$\begin{matrix} CH_3{\cdot}C{\cdot}OK \\ \| \\ CH_3{\cdot}CO{\cdot}O{\cdot}N \end{matrix} \rightarrow \begin{matrix} CH_3{\cdot}CO{\cdot}O{\cdot}C{\cdot}OK \\ \| \\ CH_3{\cdot}N \end{matrix} \rightarrow CH_3{\cdot}N{=}C{=}O + CH_3{\cdot}CO{\cdot}OK$$

$$2\,CH_3{\cdot}N{=}C{=}O + H_2O = (CH_3{\cdot}NH)_2C{=}O + CO_2.$$

The aromatic hydroxamic acids, such as benzhydroxamic acid, $\phi{\cdot}C\langle^{OH}_{NOH}$ (from benzoyl chloride and hydroxylamine, or by the oxidation of benzaldoxime, &c.), closely resemble the alkyl compounds.

The ethers (or esters) of the hydroxamic acids can exist in several isomeric forms. For example, if formic ester is treated with an α-(O–)-hydroxylamine, it gives a hydroxamic ether in which the hydrogen of the hydroxylamine OH is replaced[4]:—

$$H{\cdot}C\langle^{O}_{OR} + H_2N{\cdot}OEt \rightarrow H{\cdot}C\langle^{O}_{NH{\cdot}OEt} \quad \text{or} \quad H{\cdot}C\langle^{OH}_{N{\cdot}OEt}.$$

[1] L. W. Jones, *Am. Ch. J.* **20**. 1 (1898). [2] Werner, Buss, *Ber.* **28**. 1280 (1895).
[3] Wieland, *Ber.* **40**. 1676 (1907). [4] Nef, *Ber.* **31**. 2721 (1898); Biddle, *Ann.* **310**. 9 (1899).

On the other hand, if benzimido-ether is treated with hydroxylamine, an ether is formed in which the hydrogen of the other hydroxyl (COH) is replaced by alkyl:—

$$\phi\cdot C\begin{matrix}\diagup OEt\\ \diagdown NH\end{matrix} \rightarrow \phi\cdot C\begin{matrix}\diagup OEt\\ \diagdown NOH\end{matrix}.$$

(Here there is no tautomeric formula possible, as the 'wandering' hydrogen is replaced.) The ethers of this latter type all occur in two modifications (when derived from the aromatic hydroxamic acids), which must be stereo-isomers of the type of the syn- and anti-oximes:—

$$\alpha\ (\text{syn})\ \begin{matrix}\phi\cdot C\cdot OEt\\ \|\\ HO\cdot N\end{matrix} \qquad \beta\ (\text{anti})\ \begin{matrix}\phi\cdot C\cdot OEt\\ \|\\ N\cdot OH\end{matrix}.$$

This is confirmed by the fact that the α-(syn)-ethers, when treated with phosphorus pentachloride, undergo the Beckmann change, and are converted into phenyl-carbamic acids:—

$$\begin{matrix}\phi\cdot C\cdot OEt\\ \|\\ HO\cdot N\end{matrix} \rightarrow \begin{matrix}HO\cdot C\cdot OEt\\ \|\\ \phi\cdot N\end{matrix} \rightarrow \begin{matrix}O:C\cdot OEt\\ |\\ \phi\cdot NH\end{matrix},$$

while the β-(anti)-ethers do not react in this way, but form phosphoric esters.[1]

AMIDOXIMES

These are related to the hydroxamic acids in the same way as the amidines to the amides: they are oxy-amidines $R\cdot C\begin{matrix}\diagup NOH\\ \diagdown NH_2\end{matrix}$ or $R\cdot C\begin{matrix}\diagup NH\cdot OH\\ \diagdown NH\end{matrix}$. The first formula agrees best with their behaviour. The first member of the group (formamidoxime or isuretin) was discovered by Lossen;[2] the whole group was subsequently investigated by Tiemann[3] and his pupils.

Their method of preparation is similar to that of the amidines. The alkyl derivatives are got by the action of hydroxylamine on the nitriles:—

$$R\cdot C{\equiv}N + H_2NOH = R\cdot C\begin{matrix}\diagdown NOH\\ \diagup NH_2\end{matrix},$$

the aromatic by the action of hydroxylamine on the thioamides, imido-ethers, and amidines.

They form stable salts with acids, unstable salts with bases. The free amidoximes are easily hydrolysed, even by water alone, to hydroxylamine and the amide. Their hydrochlorides are converted by sodium nitrite into the amide and nitrous oxide:—

$$R\cdot C\begin{matrix}\diagup NOH\\ \diagdown NH_2\end{matrix} + HNO_2 = R\cdot C\begin{matrix}\diagup O\\ \diagdown NH_2\end{matrix} + N_2O + H_2O.$$

They resemble the hydroxamic acids in many ways. When treated with phosphorus pentachloride they are converted, by the Beckmann reaction, into alkyl-ureas:—

$$\begin{matrix}R\cdot C\cdot NH_2\\ \|\\ HO\cdot N\end{matrix} \rightarrow \begin{matrix}HO\cdot C\cdot NH_2\\ \|\\ R\cdot N\end{matrix} \rightarrow \begin{matrix}O{=}C\cdot NH_2\\ |\\ R\cdot N\cdot H\end{matrix}.$$

[1] Werner, *Ber.* **29.** 1146 (1896).
[2] *Ann. Spl.* **6.** 234 (1868).
[3] *Ber.* **17.** 126, 1685 (1884); **22.** 2391 (1889), &c.

Formamidoxime $HC\begin{matrix}NOH\\NH_2\end{matrix}$, also known as isuretin, being an isomer of urea, is a solid melting at 114–115°, which has a strong alkaline reaction.

Oxy-amidoximes or hydroxamoximes, $R{\cdot}C\begin{matrix}NOH\\NH{\cdot}OH\end{matrix}$, are also known, being obtained, for example, from hydroxylamine and a hydroxamic chloride.

OXIMES OR ISONITROSO-COMPOUNDS

The most important and numerous class of hydroxylamine derivatives are the oximes, containing the group $>C{=}NOH$.

There are two chief methods of preparing the oximes. The first and most general is by the action of hydroxylamine on a compound containing a carbonyl group—an aldehyde or a ketone. The reaction is quite general, and may be taken as a criterion of an aldehydic or ketonic grouping. The number of instances in which it does not occur is very small.

It is usually carried out by warming the aldehyde or ketone in aqueous or dilute alcoholic solution with hydroxylamine hydrochloride and an equivalent of sodium carbonate :—

$$R{\cdot}C\begin{matrix}H\\O\end{matrix} + H_2NOH = H_2O + R{\cdot}C\begin{matrix}H\\NOH\end{matrix}.$$

This generally suffices for aldehydes, but many ketones require a more energetic treatment, such as heating in a sealed tube with excess of soda.

The velocity of formation of oximes by this method has been investigated by Petrenko-Kritschenko and Kautscheff.[1] They used N/1000 solutions in 50 per cent. aqueous alcohol. They did not determine the velocity constant, but only measured the amount of oxime formed in a given time by removing a sample and titrating the unchanged hydroxylamine either with iodine, or with hydrochloric acid, using *p*-nitro-phenol as indicator. Their chief results were as follows:—

1. The order of velocities of formation of oxime with hydroxylamine is roughly the same as that of the formation of hydrazones and of the bisulphite compounds.

2. Among the ketones, those with a methyl attached to the carbonyl react most rapidly, those with larger alkyls (especially secondary) more slowly.

3. Ring ketones (such as keto-cyclohexane) form oximes very rapidly, and those with 6-rings very much quicker than those with 5- or 7-rings.

4. Aromatic ketones react more slowly than fatty, aromatic aldehydes more quickly than fatty.

5. In the keto-acids, the substitution of CO_2Et for CH_3 diminishes the velocity, and the more so the further it is from the carbonyl. Also the replacement of ethyl for hydrogen diminishes the velocity. The reaction is reversible. It is catalysed to some extent by acids, and much more so by alkalies.[2]

[1] *Ber.* **39**. 1452 (1906). Very similar results were obtained in aqueous solution by Stewart, *J. C. S.* **1905**. 410.

[2] Acree, *Am. Ch. J.* **39**. 300 (*C.* **08**. i. 1389).

The second main method for preparing oximes is by the action of nitrous acid on the methylene group CH_2. This is the exact converse of the first:—

$$\left.\begin{array}{l} >C{=}O + H_2NOH \\ >C{:}H_2 + O{:}NOH \end{array}\right\rangle >C{=}NOH + H_2O.$$

It is not all methylene groups which will react with nitrous acid, but only those whose hydrogen has acquired a more or less acidic character from the proximity of negative groups. Thus aceto-acetic ester gives the so-called isonitroso-aceto-acetic ester:—

$$CH_3{\cdot}CO{\cdot}\underset{CO{\cdot}OEt}{CH_2} + O{:}NOH = CH_3{\cdot}CO{\cdot}\underset{CO{\cdot}OEt}{C{=}NOH} + H_2O.$$

The nomenclature of these bodies is rather confusing. It is to be noticed that there is no difference between the oxime and the isonitroso grouping. The distinction has reference only to the way in which the body is derived from its mother substance. Take acetone as an example. Its oxime, $CH_3{\cdot}C(:NOH)CH_3$, is derived from it by replacing the ketonic oxygen by $=NOH$: while in isonitroso-acetone the $=NOH$ replaces two hydrogens attached to one carbon, $CH_3{\cdot}CO{\cdot}CH{:}NOH$. Hence the difference of name indicates a real difference of constitution; but it would be equally correct to call acetoxime isonitroso-propane, and isonitroso-acetone methyl-glyoxal monoxime.

There is a third method of preparing the oximes which is of great theoretical interest. This is Scholl's reaction,[1] a modification of that of Friedel and Crafts. It consists in treating an aromatic hydrocarbon with mercury fulminate in presence of a mixture of hydrated and anhydrous aluminium chloride. We may suppose that in this reaction the water liberates hydrochloric acid, which sets free fulminic acid. This, as will be shown later, has the formula $C{=}NOH$. It combines with more hydrochloric acid to give formyl chloride oxime $\overset{H}{Cl}\!>\!C{=}NOH$; and this reacts with the aromatic hydrocarbon in the normal Friedel and Crafts manner:—

$$C_6H_5{\cdot}H + \overset{Cl}{H}\!>\!C{=}NOH = HCl + \overset{C_6H_5}{H}\!>\!C{=}NOH.$$

The actual product is therefore benzaldoxime. Unless a partially hydrated aluminium chloride is used, the product body obtained is a dehydration-product of benzaldoxime, benzonitrile.

The oximes can also be prepared by the reduction of the nitro-compounds and by the oxidation of the amines.

The oximes are at once feebly basic and feebly acidic. They dissolve in alkalies, and also form salts in ethereal solution with mineral acids. They are, however, only in a secondary sense amphoteric electrolytes. The hydrogen ion to which the acidic properties are due is derived directly from the oxime:—

$$R_2C{=}NOH \rightleftharpoons R_2C{=}NO' + H',$$

while the basic properties are due to the nitrogen becoming pentad, as in the salt $R_2C{=}NH(OH)Cl$.

[1] *Ber.* **36**, 10 (1903).

When the oximes are warmed with acids they break up again into hydroxylamine and the aldehyde or ketone, the reaction by which they are formed being reversible:—

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{=}O + H_2NOH \rightleftharpoons \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{=}NOH + H_2O.$$

In this particular case equilibrium is attained from either side (in presence of one equivalent of mineral acid) when about two-thirds of the acetone has been converted into oxime; and this equilibrium is very little affected by the temperature.[1]

The ketoximes when treated with sodium ethylate are converted into ethers, such as $(CH_3)_2C{:}NO{\cdot}Et$, which on hydrolysis with acids yield the α-hydroxylamines, as H_2NOEt.[2]

The ketoximes are converted by acetic anhydride into their acetic esters, the oxime hydrogen being replaced by acetyl:—

$$R_2C{:}NOH \longrightarrow R_2C{:}NO{\cdot}CO{\cdot}CH_3.$$

But most aldoximes do not give this reaction, the anhydride acting merely as a dehydrating agent and forming the nitrile:—

$$R{\cdot}C\!\begin{matrix}H\\\diagdown\!\diagup\\NOH\end{matrix} = R{\cdot}C{\equiv}N + H_2O.$$

If treated with acetyl chloride many oximes undergo the remarkable Beckmann reaction, the nitrogen inserting itself into the middle of the chain to give a substituted amide:—

$$\begin{matrix}CH_3{\cdot}C{\cdot}CH_3\\\|\\N{\cdot}OH\end{matrix} \longrightarrow \begin{matrix}CH_3{\cdot}C{:}O\\|\\HN{\cdot}CH_3\end{matrix}.$$

On reduction with sodium amalgam in dilute acetic acid,[3] or electrolytically in presence of strong sulphuric acid, or with calcium turnings in alkaline solution in presence of mercuric chloride,[4] they are converted into amines. The electrolytic method has been used commercially, for example, for the preparation of isopropylamine[5]:—

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{=}NOH + 2\,H_2 = \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C\!\begin{matrix}H\\\diagdown\!\diagup\\NH_2\end{matrix} + H_2O.$$

On oxidation (with Caro's acid) the oximes undergo two changes.[6] In the first place the CH group is oxidized to COH, giving a hydroxamic acid:—

$$\phi{\cdot}CH{=}NOH + O = \phi{\cdot}C\!\begin{matrix}OH\\\diagdown\!\diagup\\NOH\end{matrix}.$$

This is the common behaviour of hydrogen attached to a carbon which carries no other hydrogen, as in the oxidation of aldehydes to acids. At the same time part of the oxime is oxidized in a different way, giving a nitro-compound:—

$$\phi{\cdot}C\!\begin{matrix}H\\\diagdown\!\diagup\\NOH\end{matrix} + O = \phi{\cdot}C\!\begin{matrix}H\\\diagdown\!\diagup\\N\\\diagup\!\diagdown\\OH\end{matrix}\!\!O \longrightarrow \phi{\cdot}CH_2{\cdot}N\!\begin{matrix}O\\\diagup\!\diagdown\\O\end{matrix}.$$

[1] Francesconi, Milesi, *C.* **02.** ii. 259.

[2] The velocity of etherification of the oximes has been examined by Goldschmidt, *Z. f. Elektrochem.* **14.** 581 (*C.* **08.** ii. 1351).

[3] Tafel, Pfeffermann, *Ber.* **35.** 1510 (1902).

[4] Beckmann, *Ber.* **38.** 904 (1905).

[5] *C.* **03.** i. 1162.

[6] Bamberger, *Ber.* **33.** 1781 (1900).

Formaldoxime,[1] if it is rapidly prepared, can be obtained in the monomolecular form as a liquid, $H_2C{=}NOH$, boiling at 84–5°; but this rapidly changes to a polymer, probably $(H_2CNOH)_3$, a gelatinous body insoluble in organic solvents, but soluble in acids. If this polymer is heated it volatilizes, giving a vapour whose density shows it to be monomolecular. If it is carefully heated in a test tube, liquid drops of the simple oxime are deposited on the sides of the tube; but they change almost immediately into the solid polymer. In this strong tendency to polymerize formaldoxime resembles formaldehyde itself.

On sudden heating formaldoxime breaks up into water and prussic acid.

Acetaldoxime, $CH_3{\cdot}CH{:}NOH$, shows signs of occurring in two modifications.[2] The ordinary form melts at 47°; but if it is kept at or above this temperature for some time, it does not freeze till much lower, and the longer it has been heated the more supercooling is required. Even when the freezing has begun the crystals only separate slowly, though they are always found to melt at 47°. This behaviour suggests that the heated liquid may be a solution of the ordinary form in one of lower melting-point.

If chloral is treated with hydroxylamine, an addition-product, $CCl_3{\cdot}CH\begin{matrix}OH\\NHOH\end{matrix}$, is first formed, which, however, readily loses water to give the oxime $CCl_3{\cdot}CH{:}NOH$. We may suppose that such an additive compound is the first product in all cases of oxime formation, though it has not been isolated in any other instance.

The oximes of diketones may be obtained in two ways. The diketone may be treated with hydroxylamine, which gives the mono- or dioxime according to the quantities employed; or the monoxime may be made (as the isonitroso-compound) by treating a mono-ketone with nitrous acid. In the latter case the oxime (isonitroso) group can often turn out another group to make room for itself. Thus, if methyl-aceto-acetic acid is treated with nitrous acid, the monoxime of diacetyl (isonitroso-ethyl-methyl-ketone) is produced:—

$$CH_3{\cdot}CO{\cdot}\underset{\displaystyle COOH}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}H + O{:}NOH = CH_3{\cdot}CO{\cdot}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}NOH + CO_2 + H_2O.$$

When the product is boiled with acids it splits off the NOH in the normal manner, and diacetyl is formed:—

$$CH_3{\cdot}CO{\cdot}C(:NOH)CH_3 + H_2O = CH_3{\cdot}CO{\cdot}CO{\cdot}CH_3 + H_2NOH.$$

Thus, by the successive action of nitrous acid and hydrolysis a CH_2 group is converted into CO, the nitrous acid being reduced to hydroxylamine. In the same way aceto-acetic acid itself gives isonitroso-acetone and carbon dioxide, while aceto-acetic ester does not split off the carboxyl, but forms its own isonitroso-derivative: and acetone-dicarboxylic acid gives di-isonitroso-acetone:—

$$\begin{matrix}CH_2{\cdot}COOH\\|\\CO\\|\\CH_2{\cdot}COOH\end{matrix} + \begin{matrix}O{:}NOH\\\\\\\\O{:}NOH\end{matrix} = \begin{matrix}CH{:}NOH\\|\\CO\\|\\CH{:}NOH\end{matrix} + 2\,H_2O + 2\,CO_2.$$

[1] Cf. Dunstan, Bossi, *J. C. S.* **1898.** 353.

[2] Dunstan, Dymond, *J. C. S.* **1894.** 206; Carveth, *C.* **98.** ii. 178; Dutoit, Fath, *C.* **04.** i. 256.

It is to be noticed that all those compounds which contain at once a carbonyl and a C=NOH group dissolve in alkali to form a deep yellow solution, whereas if all the keto-groups are converted into oxime, the alkaline solution is colourless. Thus di-isonitroso-acetone, CH(:NOH)CO·CH=NOH, gives a reddish yellow alkaline solution. Hydroxylamine converts this body into tri-isonitroso-propane, CH(:NOH)C(:NOH)CH:NOH, whose alkaline solution is colourless. There can be little doubt that this is due to the fact that the bodies of the former class (α-keto-oximes) are pseudo-acids: that their alkaline salts are derived from a tautomeric form. Thus the colourless iso-nitroso-acetone is $CH_3{\cdot}CO{\cdot}C\langle^{H}_{NOH}$; but in the alkaline salt some kind of interaction must occur between the carbonyl and the oxime groups, which we may represent by the formula $\begin{matrix}CH_3{\cdot}C{-}O\\ \quad|\quad\ |\\ HC{-}NO\end{matrix}\Big\rangle K$, as in the formation of the chromo-salts of the α-nitroketones, the dinitroparaffins, and the nitrophenols. If all the ketone groups are converted into oxime groups this particular form of tautomerism is no longer possible.

In the aromatic series, however, the dioximes of α-diketones (α-quinones) show a similar tautomeric behaviour.[1] The α-quinones of benzene, naphthalene, and phenanthrene are themselves red, and their dioximes yellow. These dioximes all form anhydrides, $\begin{matrix}-C{=}N\\ \quad|\\ -C{=}N\end{matrix}\Big\rangle O$, which are colourless. Their ethers, $\begin{matrix}-C{=}NOAlk\\ \quad|\\ -C{=}NOAlk\end{matrix}$, in the naphthalene series are yellow, and in the phenanthrene series colourless. The salts, as $\begin{matrix}-C{=}NONa\\ \quad|\\ -C{=}NONa\end{matrix}$, are dark red in the benzene derivatives, yellow in those of naphthalene, and nearly colourless in those of phenanthrene. Such facts as these show the weakness of the 'quinoid' theory of colour: for all these compounds, as usually written, contain the same quinoid ring. We must suppose an equilibrium between two tautomeric forms, one colourless, no doubt the simple quinoid form, and the other coloured, in which the two oxime groups interact:—

$$Ar\langle^{NOX}_{NOX} \rightleftharpoons Ar\langle^{NOX}_{NOX}.$$

Colourless Coloured

The first structure will be that of the anhydrides, and will predominate in the free oximes: the salts will mainly consist of the second.

STEREOISOMERISM OF THE OXIMES

The study of the aromatic oximes led to the discovery of the stereoisomerism of trivalent nitrogen.[2] The question was opened by the discovery of V. Meyer and Goldschmidt (1883-8) that benzil dioxime, $\phi{\cdot}C{:}NOH{\cdot}C{:}NOH{\cdot}\phi$, exists in two isomeric forms. The investigation of their properties showed that they must

[1] Schmidt, Söll, *Ber.* **40.** 2454 (1908); Hantzsch, Glover, ib. 4344.

[2] The earlier history of this subject is well given by Lachman, *The Spirit of Organic Chemistry* (1899).

both have the same structural formula. They are both hydrolysed by acids to form benzil, and therefore have the carbon chain unaltered; they both yield on oxidation the same body, $\begin{matrix}\phi\cdot C{=}N{-}O\\ |\\ \phi\cdot C{=}N{-}O\end{matrix}$, and they both have the same molecular weight. It is interesting to notice that this was the first application of Raoult's cryoscopic method in organic chemistry—a method afterwards improved by Beckmann in connexion with the same subject.

Since structural isomerism was excluded, it was natural to suggest stereoisomerism. But in benzil dioxime stereoisomerism of the carbon is impossible unless we suppose that the two central carbon atoms are incapable of free rotation about the line joining their centres of gravity. In that case there are two possible arrangements:—

$$\begin{matrix}\phi\\ \diagdown\\ \quad C{=}NOH\\ \quad |\\ \phi\diagup C{=}NOH\end{matrix} \quad \text{and} \quad \begin{matrix}\quad\quad\phi\\ \quad\quad\diagup\\ HON{=}C\\ \quad\quad |\\ \phi\diagup C{=}NOH\end{matrix}.$$

But van 't Hoff's second law, which is supported by an enormous mass of evidence, declares that with two singly linked carbon atoms free rotation must be possible; and no parallel case of stereoisomerism of this kind could be adduced. If, however, the assumption is made, it is easy to show that three isomeric dioximes of benzil and three monoximes are possible; and when, in 1889, V. Meyer and Auwers actually discovered a third dioxime and a second monoxime, it seemed as if this hypothesis must be accepted.

Meanwhile, in 1886, Beckmann had found that benzaldoxime, ϕ·CH:NOH, could be converted into an isomer. Here the explanation offered for the benzil derivatives is impossible, because there is no second carbon atom; and hence chemists adopted the theory that the second oxime had the formula $\phi\cdot\begin{matrix}CH{-}NH\\ \diagdown\ \diagup\\ \quad O\end{matrix}$.

This theory soon received apparent confirmation from the following discovery. If the two benzaldoximes are treated with benzyl iodide and alkali, they are converted into two isomeric benzyl ethers, which, according to the received formulae of the oximes, should be

$$\phi\cdot CH{:}NO\cdot CH_2\cdot\phi \quad \text{and} \quad \phi\cdot\begin{matrix}CH{-}N\cdot CH_2\cdot\phi,\\ \diagdown\ \diagup\\ \quad O\end{matrix}$$

and it was shown that they actually had these formulae by the fact that on hydrolysis one gave α-benzyl-hydroxylamine, $H_2N\cdot OCH_2\cdot\phi$, and the other β-, $HN\begin{matrix}\diagup CH_2\cdot\phi\\ \diagdown OH\end{matrix}$.

But before long this view was overthrown by the work of Goldschmidt. He investigated first the behaviour of the benzil oximes with phenyl isocyanate, ϕ·N:C:O. This body reacts readily both with OH and with NH groups. With hydroxyl compounds it gives urethane derivatives; for example, with alcohol, phenyl urethane:—

$$\begin{matrix}\phi\cdot N{=}C{=}O\\ +\quad HO\cdot Et\end{matrix} = \begin{matrix}\phi\cdot NH\\ \diagdown\\ \quad C{:}O.\\ \diagup\\ EtO\end{matrix}$$

With imine groups it gives substituted ureas; e. g. with diethylamine, diethylphenyl urea:—

$$\phi\cdot NH\diagdown C{:}O\diagup NEt_2 \quad = \quad \phi\cdot NH\diagdown C{:}O.\diagup Et_2N$$

Hence phenyl isocyanate should react differently with the oximes according as they are R·CH:NOH or R·CH(—O—)NH. Goldschmidt found, however, that the two isomeric benzil monoximes gave the same product with this reagent; and so also did the three benzil dioximes. This was in accordance with the views of V. Meyer and Auwers, who regarded these isomers as structurally identical. But on applying the same reagent to the two benzaldoximes, Goldschmidt found that they too gave identical products, which was inconsistent with Beckmann's view that the benzaldoximes were structural isomers. And Goldschmidt pointed out that his evidence was much stronger than Beckmann's evidence on the other side; for Beckmann had only shown that the benzyl ethers were structurally different; and we know of many cases where the same mother substance gives two series of ethers.

Thus it was shown that the benzaldoximes, like the benzil oximes, were structurally identical; while the hypothesis of the absence of free rotation, brought forward to explain the isomerism of the benzil derivatives—a hypothesis which was even there of doubtful validity—was wholly inapplicable to the case of the benzaldoximes.

At this point Hantzsch and Werner brought out a paper of fundamental importance,[1] in which they offered a solution of the whole problem which has since been universally accepted. The novelty of their hypothesis consists in this, that the stereoisomerism is referred not to the carbon, but to the nitrogen, or rather to the two together. In the ordinary case of triad nitrogen, where the nitrogen is united to three different monovalent groups, it is most natural to suppose that the three valencies are equally distributed in a plane, which would make stereoisomerism impossible. But there are many compounds in which a triad nitrogen atom replaces a CH group, as in the series $\begin{matrix}CH\\|\\|\\CH\end{matrix}\ \begin{matrix}CH\\|\\|\\N\end{matrix}\ \begin{matrix}N\\|\\|\\N\end{matrix}$, or in benzene and pyridine. In such cases it seems possible that the three nitrogen valencies may be arranged in the same way as the three free valencies of the carbon in CH; that is, in the directions from the centre towards three angles of a tetrahedron. This is the hypothesis which Hantzsch and Werner suggest: they represent the three nitrogen valencies as directed towards three angles of a tetrahedron, of which the nitrogen atom itself occupies the fourth angle. Thus, a compound with doubly linked triad nitrogen of the general formula $\begin{matrix}X\\Y\end{matrix}\!\!>\!C{=}N\cdot Z$ may occur in two stereo-modifications:—



[1] *Ber.* **23**. 11 (1890).

which for the sake of brevity may be written

$$\begin{matrix} X\cdot C\cdot Y \\ \| \\ N\cdot Z \end{matrix} \quad \text{and} \quad \begin{matrix} X\cdot C\cdot Y \\ \| \\ Z\cdot N \end{matrix} .$$

The case is exactly parallel to that of the double-link carbon isomerism, as in fumaric and maleic acids, where the general type is

$$\begin{matrix} a\cdot C\cdot b \\ \| \\ a\cdot C\cdot b \end{matrix} \quad \text{and} \quad \begin{matrix} a\cdot C\cdot b \\ \| \\ b\cdot C\cdot a \end{matrix} .$$

The truth of this theory was finally established by three further discoveries.

In the first place, it was found that in many cases the benzoyl and acetyl esters of the oximes can exist in three forms. One of these is the N-ester; but the others are both O-esters, and must be stereoisomeric, since there is no other possibility.

Secondly, the occurrence of stereoisomeric oximes has been found to depend on the two groups attached to the carbon being different. It is obvious that on Hantzsch and Werner's scheme, if X and Y are identical, no isomerism can occur, and the facts have been shown to agree with this. Even the slightest difference between the two groups is sufficient to cause isomerism, but unless some such difference occurs, no isomers are obtained. Thus benzophenone oxime, $\begin{matrix} \phi\cdot C\cdot\phi \\ \| \\ N\cdot OH \end{matrix}$, only occurs in one form, whereas of *p*-chloro-benzophenone oxime there are two, $\begin{matrix} \phi\cdot C\cdot C_6H_4Cl \\ \| \\ N\cdot OH \end{matrix}$ and $\begin{matrix} \phi\cdot C\cdot C_6H_4Cl \\ \| \\ HO\cdot N \end{matrix}$.

Thirdly, it has been found possible to assign to the various isomers their stereo-formulae in a consistent manner. The considerations employed in determining them are as follows:—

To begin with, a nomenclature is required for these compounds. For this purpose Hantzsch and Werner use the prefixes *syn-* and *anti-*, the former denoting that the hydroxyl is near to, and the latter that it is remote from, that group (of X and Y) which immediately follows the prefix. Thus the body, $\begin{matrix} \phi\cdot C\cdot C_6H_4\cdot CH_3 \\ \| \\ HO\cdot N \end{matrix}$, may be called syn-phenyl-tolyl-ketoxime, or anti-tolyl-phenyl-ketoxime. When one of the groups reacts with the hydroxyl, as in the aldoximes (which can give nitriles), the name is so chosen that the reactive form is called syn; thus of the two benzaldoximes:—

(Reactive) $\begin{matrix} \phi\cdot C\cdot H \\ \| \\ N\cdot OH \end{matrix}$	(Not reactive) $\begin{matrix} \phi\cdot C\cdot H \\ \| \\ HO\cdot N \end{matrix}$
Benz-synaldoxime	Benz-antialdoxime
(not anti-benzaldoxime)	(not syn-benzaldoxime)

The dioximes of the symmetrical diketones can occur in three forms, distinguished as syn, anti, and amphi:—

syn $\begin{matrix} -C- \\ \| \\ N\cdot OH \end{matrix} \quad \begin{matrix} -C- \\ \| \\ HO\cdot N \end{matrix}$, anti $\begin{matrix} -C- \\ \| \\ HO\cdot N \end{matrix} \quad \begin{matrix} -C- \\ \| \\ N\cdot OH \end{matrix}$, amphi $\begin{matrix} -C- \\ \| \\ N\cdot OH \end{matrix} \quad \begin{matrix} -C- \\ \| \\ N\cdot OH \end{matrix}$.

In determining which configuration is to be assigned to each of the two

isomers, we rely mainly on two reactions. The first of these, which applies to the aldoximes alone, is the formation of nitriles. For example, the two benzaldoximes can easily be converted into acetyl derivatives, which are readily saponified, and so must have the acetyl attached to oxygen, not nitrogen: and which can be readily turned into one another, and therefore must be stereo- and not structural isomers. Their formulae are therefore:—

$$\phi\cdot C\cdot H \quad \text{and} \quad \phi\cdot C\cdot H$$
$$\| \qquad\qquad\qquad\qquad \|$$
$$N\cdot O\cdot CO\cdot CH_3 \qquad CH_3\cdot CO\cdot O\cdot N$$

On gentle warming with sodium carbonate one of these esters forms benzonitrile:—

$$\begin{matrix}\phi\cdot C\cdot H\\ \|\\ N\cdot O\cdot CO\cdot CH_3\end{matrix} = \phi\cdot C{\equiv}N + CH_3\cdot CO\cdot OH,$$

while the other gives no nitrile, but only regenerates the original oxime by saponification. Hence the first must be the syn-compound, derived from benz-synaldoxime, since this has the hydrogen and the $O\cdot CO\cdot CH_3$ close together; while the second must be the anti-body.

With the ketoximes we cannot use this method, and we have to rely on the Beckmann intramolecular transformation. In this strange reaction, which is brought about, often at the ordinary temperature, by various reagents, of which acetyl chloride, phosphorus pentachloride, and concentrated sulphuric acid are the most commonly used, the oxime is converted into a substituted amide. Thus benzophenone oxime gives phenyl benzamide (benzanilide):—

$$\begin{matrix}\phi\cdot C\cdot\phi\\ \|\\ N\cdot OH\end{matrix} = \phi\cdot CO\cdot NH\cdot\phi.$$

The reaction is most simply explained as consisting in an exchange of the hydroxyl with one of the groups attached to the carbon:—

$$\begin{matrix}X\cdot C\cdot X\\ \|\\ N\cdot OH\end{matrix} \rightarrow \begin{matrix}X\cdot C\cdot OH\\ \|\\ N\cdot X\end{matrix} \rightarrow \begin{matrix}X\cdot C\cdot O\\ |\\ NHX\end{matrix}.$$

If the two groups attached to the carbon are different, it can go in two ways:—

$$\begin{matrix}X\cdot C\cdot Y & \nearrow X\cdot CO\cdot NHY\\ \|\\ N\cdot OH & \searrow Y\cdot CO\cdot NHX\end{matrix}.$$

Thus, wherever stereoisomerism is possible, it is also possible to get two products in the Beckmann reaction. It is evident that, if our interpretation of the nature of the isomerism and of the nature of the Beckmann reaction is correct, the group which becomes attached to the nitrogen is that which was in the syn-position to the hydroxyl in the original oxime, e. g.:—

$$\begin{matrix}X\cdot C\cdot Y\\ \|\\ N\cdot OH\end{matrix} \rightarrow \begin{matrix}X\cdot C\cdot OH\\ \|\\ N\cdot Y\end{matrix} \rightarrow \begin{matrix}X\cdot C{=}O\\ |\\ NHY\end{matrix}.$$

$$\begin{matrix}X\cdot C\cdot Y\\ \|\\ HO\cdot N\end{matrix} \rightarrow \begin{matrix}HO\cdot C\cdot Y\\ \|\\ X\cdot N\end{matrix} \rightarrow \begin{matrix}O{=}C\cdot Y\\ |\\ NHX\end{matrix}.$$

Now it is found that in all cases of stereoisomeric ketoximes one form gives

only one product in the Beckmann reaction, while the second form gives some of this product, but mainly the other. This only means that the second isomer is less stable than the first, and in the course of the reaction is partly converted into it. It does not prevent us from drawing conclusions as to the spatial configurations of the two forms from the products of the reaction. For example, one of the phenyl-tolyl-ketoximes gives only toluic anilide, whence we can infer that it has the hydroxyl and the phenyl in the syn-position:—

$$CH_3\cdot C_6H_4\cdot \underset{\underset{N\cdot OH}{\|}}{C}\cdot\phi \rightarrow CH_3\cdot C_6H_4\cdot \underset{\underset{N\cdot\phi}{\|}}{C}\cdot OH \rightarrow CH_3\cdot C_6H_4\cdot \underset{\underset{NH\phi}{|}}{C}{=}O;$$

while the other gives some of this, but mainly the toluidide of benzoic acid, so that it must be the anti-phenyl compound:—

$$CH_3\cdot C_6H_4\cdot \underset{\underset{HO\cdot N}{\|}}{C}\cdot\phi \rightarrow HO\cdot \underset{\underset{CH_3\cdot C_6H_4\cdot N}{\|}}{C}\cdot\phi \rightarrow O{=}\underset{\underset{CH_3\cdot C_6H_4\cdot N\cdot H}{|}}{C}\cdot\phi.$$

By means of these two reactions—the formation of nitrile with the aldoximes and the Beckmann reaction with the ketoximes—we can assign stereo-formulae to all the known isomeric oximes.

Now although there are no known cases of isomerism where the two groups attached to the carbon are the same, yet there are many cases in which they are different, where isomers cannot be obtained. And these cases occur not at haphazard, but regularly, in particular classes of oximes. Thus, nearly all aldoximes in which the CH:NOH group is directly attached to the benzene nucleus give isomers; but they are not obtained with the mixed (aryl-alkyl) ketoximes, such as acetophenone oxime. This is no objection to the theory of Hantzsch and Werner; it indicates that one isomer is so unstable that it changes spontaneously into the other: which is confirmed by the fact that in all cases of this kind—where only one solid form is known—it gives only a single product in the Beckmann reaction, showing that it consists wholly of one isomer. Thus, when the mixed ketoximes are submitted to the Beckmann reaction, it is always the aromatic group which migrates to the nitrogen, proving the oxime is the syn-aromatic body; e. g. that acetophenone oxime is $\underset{\underset{HO\cdot N}{\|}}{\phi\cdot C}\cdot CH_3$.

The unsymmetrical purely aliphatic ketoximes, which also give no isomers, are oils; when treated by Beckmann's method they give a mixture of the two possible amides, and are therefore, no doubt, themselves mixtures of the isomeric oximes. This affords a good example of the general rule for tautomeric substances, first laid down by Knorr, that a solid tautomeric body must consist wholly of one form, while a liquid tautomer must always be a mixture of the two.

The greater stability of one form of an unsymmetrical oxime is an indication that the hydroxyl of the oxime group is more strongly attracted by one of the groups attached to the carbon than by the other; and from an extensive study of these compounds Hantzsch has compiled a list of radicals in the order in which they attract the hydroxyls: so that if an oxime has attached to the

carbon two of these groups, the more stable isomer will have the hydroxyl on the same side as the radical higher on the list:—

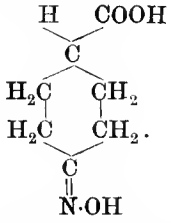
1. $-CH_2\cdot COOH$ (strongest attraction for hydroxyl).
2. $-CH_2\cdot CH_2\cdot COOH$.
3. $-COOH$.
4. $-C_6H_5$.
5. $-C_6H_4X$ (meta or para).
6. $-CO\cdot\phi$.
7. $-C_6H_4X$ (ortho).
8. $-C_4H_3S$ (thienyl, the thiophene residue).
9. $-C_nH_{2n+1}$ $(n>1)$.
10. $-CH_3$.

In the case of any ketoxime, the chance of getting isomers is greater the nearer the two radicals stand on the list, since the 'preferential' attraction of the hydroxyl is less. But it is to be noticed that this list applies only to the oximes themselves. If the hydrogen of the hydroxyl is replaced, as in the formation of an ester or a salt, these relations no longer hold.

Besides the above-mentioned cases of the purely aromatic ketoximes, some of the more complicated fatty ketoximes give isomers, and also apparently some quite simple fatty aldoximes.

Beckmann has recently announced[1] the discovery of a third modification of benzaldoxime and of certain other aromatic aldoximes. These forms are very unstable, and readily change into the usual isomers. They have not yet been fully investigated, and we may assume provisionally that they are only cases of crystalline dimorphism, like that of acetophenone.

A remarkable confirmation of the theory of Hantzsch and Werner has been afforded by the recent work of Mills and Bain.[2] They prepared the oxime of *p*-keto-hexamethylene carboxylic acid:—

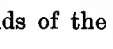


The quinine salt of this oxime-acid was separated by fractional crystallization into two parts. When one fraction was treated with soda and the quinine removed by ether, the resulting solution (of the sodium salt) showed distinct rotatory power, which, however, was destroyed by the addition of hydrochloric acid. It was thus proved that the oxime can exist in two optically active forms.

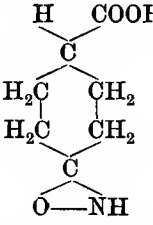
This activity is only possible if the molecule has no plane of symmetry. Now a plane perpendicular to that of the ring will pass through the carboxyl and the hydrogen attached to the same carbon atom, and also through the carbon and the nitrogen of the oxime group, the two valencies joining these last

[1] *Ber.* **37**. 3042 (1904.)

[2] *Proc. C. S.* **25**. 177 (1909).

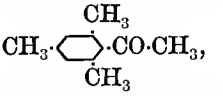
two atoms lying in this plane. Hence the remaining group, the oxime hydroxyl, must lie outside it: or, in other words, the three valencies of the nitrogen cannot lie in one plane. The asymmetry is analogous to that of carbon compounds of the type  .

This discovery incidentally disposes of the view, to which some chemists are still attached, that the isomeric oximes have the structure  . A body of the formula

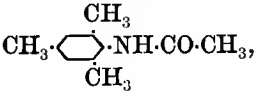


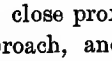
would have the hydrogen and the carboxyl, and also the oxygen and the nitrogen of the oxime, in one plane, perpendicular to that of the ring. It would thus admit of 'geometrical' isomerism (like that of the hexahydro-terephthalic acids), but not of optical activity, since it would be symmetrical.

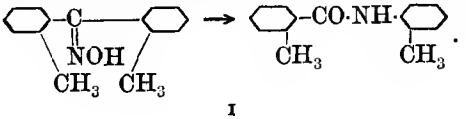
The formation of oximes offers some remarkable instances of stereo-hindrance, in which the carbonyl group of the ketone is, so to speak, blockaded by the other parts of the molecule so that the hydroxylamine cannot get at it, or not without difficulty. These occur where the carbonyl is directly attached to the benzene nucleus, and may be regarded as special cases of stereo-hindrance of the benzoic acid derivatives, as such ketones are really derived from benzoic acid. A ketone of this kind, if it has both the ortho positions on the ring occupied, will not give an oxime at all. Thus acetomesitylene,



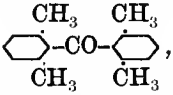
if it is heated with hydroxylamine on the water bath, does not react. If the two bodies are heated together in a sealed tube to 160°, they go at once to the product of the Beckmann reaction, acetomesidide:—



showing that at this temperature the oxime has a transient existence. Again, in benzophenone,  , the close proximity of the two phenyl groups makes the carbonyl difficult of approach, and in order to form the oxime the body must be heated on the water bath with hydroxylamine for a whole day. If one ortho position on each ring is occupied no oxime can be isolated; there is no action with hydroxylamine except under very energetic treatment, which converts the oxime as fast as it is produced into the Beckmann product:—



Finally, if all the four ortho positions on the two rings are occupied by methyl groups,



hydroxylamine has no action on the compound whatever.

As examples of the aromatic aldoximes, those of benzaldehyde may be considered.

The α-form, benz-anti-aldoxime, $\begin{matrix}\phi\cdot C\cdot H\\ \|\\ HO\cdot N\end{matrix}$, is obtained directly. It melts at 35°. If treated with hydrochloric acid in ether at 0° it forms its hydrochloride, melting at 193–195°; but at the ordinary temperature the hydrochloride of the syn-compound, melting at 66°. If the free α-oxime is treated with hydrochloric acid or sulphuric acid it is converted (through the salt) into the β-form, the syn-aldoxime.

The β-form, benz-syn-aldoxime, $\begin{matrix}\phi\cdot C\cdot H\\ \|\\ N\cdot OH\end{matrix}$, is obtained from the α by one of the above methods. It melts, when rapidly heated, at 128–130°; if it is slowly heated, or left for some time in contact with alcohol, or boiled with ether, or distilled in vacuo, it goes over into the α.

Beckmann's third modification is got by fusing the α-form and cooling rapidly to a low temperature, when it separates in crystals, melting at +5°.

The α-oxime, when dissolved in alcoholic potash, gives with benzyl iodide mainly a liquid benzyl ether, which on hydrolysis with hydrochloric acid yields benzaldehyde and α-benzyl hydroxylamine, $H_2N\cdot O\cdot CH_2\phi$, from which bodies it also can be synthesized. It is, therefore, the O-ether $\phi\cdot CH{=}N\cdot O\cdot CH_2\phi$.

The β-oxime with benzyl iodide gives mainly a solid benzyl ether, which hydrolyses to benzaldehyde and β-benzyl hydroxylamine, $HNOH\cdot CH_2\phi$, and can be synthesized from them. It therefore has the formula $\phi\cdot CH\begin{matrix}N\cdot CH_2\phi\\ |\\ O\end{matrix}$.

The oximes of anisaldehyde (*p*-methoxybenzaldehyde) are remarkable from the fact that while the syn-compound is tasteless, the anti-form, $\begin{matrix}CH_3O\cdot C_6H_4\cdot C\cdot H\\ \|\\ HO\cdot N\end{matrix}$, is intensely sweet.

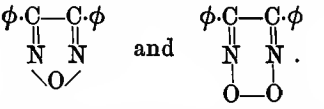
As examples of more complicated derivatives, we may consider the oximes of benzil, $\phi\cdot CO\cdot CO\cdot\phi$. There are two monoximes and three dioximes, as required by the theory. They all differ in their physical properties, and are obtained from one another by the same methods as the two benzaldoximes. Their structure is established by the following facts:—

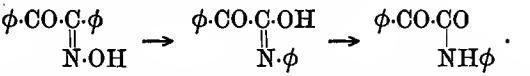
1. They are all decomposed by hydrochloric acid to give hydroxylamine and benzil, and therefore have the same carbon chain $\phi\cdot C\cdot C\cdot\phi$.

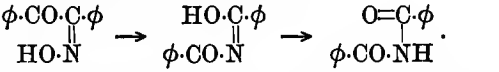
2. They yield both O- and N-ethers and esters. But the isomerism of the oximes is repeated in the O-ethers, which shows that it is stereoisomerism, since the only structural isomerism possible, that of the N-ethers, is excluded by the independent existence of these compounds.

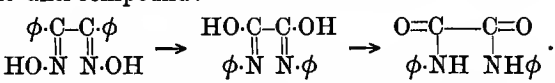
3. Further, the isomers can be converted into one another by all the means usually effective in bringing about stereo-chemical change.

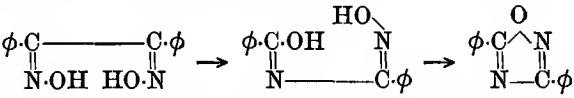
4. As regards the dioximes, their identity of structure is shown by their

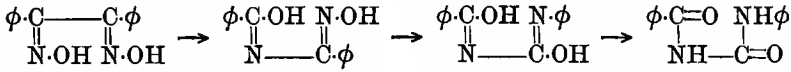
giving the same anhydride, and on oxidation with potassium ferricyanide the same peroxide:—  and .

The formulae are determined mainly, as usual, by the Beckmann reaction. The two monoximes are known as α and γ: the three dioximes as α, β, and γ. The γ-monoxime in the Beckmann reaction gives benzoyl formanilide; this indicates that it is the syn-phenyl compound:—  .

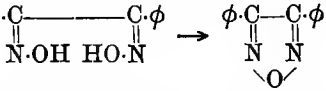
The α-oxime is the unstable one, and has a great tendency to go over into the γ; but by careful treatment it can be made to give dibenzamide, as would be expected from the anti-phenyl compound:—  .

With the dioximes the case is more complicated, and the results are less certain. The β-dioxime in the Beckmann reaction gives oxanilide; it must therefore be the anti-compound:—  .

It is less easy to determine which of the other two is syn and which is amphi. The α-dioxime gives dibenzenyl-azoxime, which has no phenyl on the nitrogen. It should therefore be the syn-compound:—  ,

while the γ gives benzoyl phenyl-urea, and so should be amphi:—  .

This formula for the γ-oxime is confirmed by the fact that it is the form produced by the direct action of hydroxylamine on the γ-monoxime  , and therefore we should expect that it must have at least one hydroxyl turned outwards.

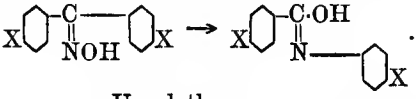
On the other hand, the γ-oxime is more easily converted into the anhydride than either of the other two; and from this we should infer that it was the syn-form:—  .

The peculiar character of the Beckmann reaction has led to various attempts being made to suggest a probable mechanism for it. It does not stand alone. There is a general tendency for compounds of the type  to go over into

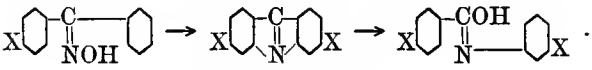
$\begin{matrix} Z\cdot C\cdot Y \\ \| \\ X\cdot N \end{matrix}$. Of this we have already met with at least three examples besides that of the oximes, namely the Hofmann reaction (amines from amides), the Curtius reaction (amines from azides), and the hydroxamic acids. In all these cases the chain is first broken and then put together again in the same unusual way. It is natural to suggest the formation of some intermediate product. Wallach[1] has proposed the series:—

$$\begin{matrix} CH_3\cdot C\cdot CH_3 \\ \| \\ N\cdot OH \end{matrix} \rightarrow \begin{matrix} CH_3\cdot C\cdot CH_2 \\ \| \quad / \\ N \end{matrix} \rightarrow \begin{matrix} CH_3\cdot C\cdot OH \\ \| \\ N\cdot CH_3 \end{matrix}.$$

This is the kind of explanation one looks for, but the point where the ring is assumed to break seems improbable, and if the theory is applied to the aromatic compounds it leads to a conclusion which has been shown to be false. For whereas on the ordinary view of a mere change of positions the oxime of a para-substituted benzophenone should give a para-anilide, on Wallach's hypothesis it should give a meta-anilide:—



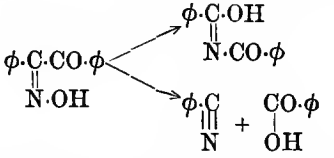
Usual theory.



Wallach's theory.

Now di-*p*-dichloro-benzophenone oxime has been found to give an anilide in which the chlorine is still in the para position,[2] which is incompatible with this view.

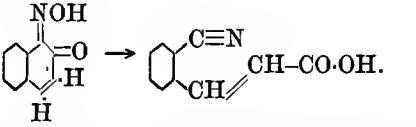
The reaction has been further examined,[3] in the case of the oximes of the α-diketones, such as benzil, by Werner and his pupils. They used benzene sulphonic chloride as the reagent to bring about the change, and showed that it would act in presence of aqueous alkali, and even in pyridine solution. They further showed that the reaction could take place in two ways; for example, with the (α) anti-phenyl monoxime of benzil:—



Type I (normal).

Type II.

In the case of the monoximes of the cyclic diketones, such as nitroso-β-naphthol, benzene sulphonic chloride in pyridine solution always causes a reaction of the second kind:—

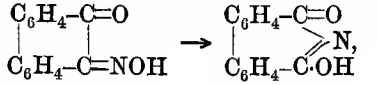


[1] *Ann.* **346.** 266.

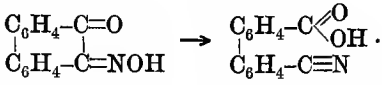
[2] Montagne, *Rec. Trav.* **25.** 376 (*C.* **07.** i. 474).

[3] Werner, Piguet, *Ber.* **37.** 4295 (1904); Werner, Detscheff, *Ber.* **38.** 69 (1905).

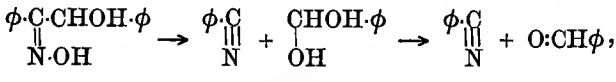
In the same way the monoxime of phenanthrene quinone, which in acid solution undergoes the normal Beckmann change (type I):—



in pyridine solution gives the reaction of type II:—



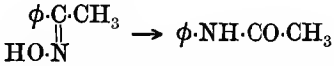
So too the α- (anti-phenyl) oxime of benzoin gives benzo-nitrile and benzaldehyde:—



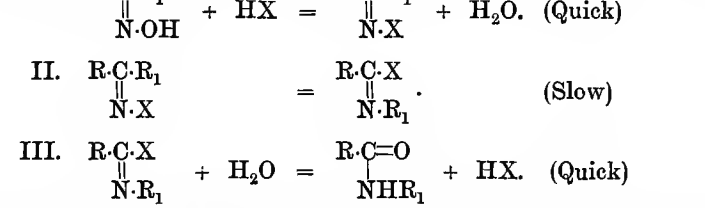
while the β-oxime gives the normal reaction. This reaction is not confined to the oximes of α-diketones, but occurs also, for example, with camphor oxime.

The occurrence of this second type of Beckmann reaction seems to indicate that an intermediate compound, such as Wallach supposes, is not required; but that the two groups on the same side of the C=N are actually split off as such, and may either go back again in the reverse order (normal reaction, type I), or may combine with one another (type II).[1]

The dynamics of the Beckmann reaction have been investigated by Sluiter,[2] who examined the change of acetophenone oxime into acetanilide in presence of sulphuric acid:—



He finds that the reaction takes place in three stages (HX = acid):—



So that the velocity measured is that of reaction II. It was determined (at 60–65°) by pouring the solution after a definite time into water, distilling it, and titrating the acetic acid which came over. The reaction was shown to be monomolecular, the temperature coefficient being about 3 for 10 degrees. The velocity depends largely on the concentration of the sulphuric acid. Thus at 60° an acid of 99·2 per cent. converts nearly the whole in 15 minutes, an acid of 93·6 per cent. only half in 275 minutes.

[1] A similar change in the case of diacetyl monoxime is given by Diels and Stern, *Ber.* **40.** 1622, 1629 (1907).

[2] *Rec. Trav.* **24.** 372 (*C.* **05.** ii. 1178).

CHAPTER VI

NITROSO-COMPOUNDS

The nitroso-compounds, properly so called, contain the grouping –N=O attached to carbon. (The nitrosamines, in which the –N=O is joined to nitrogen, will be dealt with later.) They are not a large group, but they present many interesting peculiarities.

FATTY NITROSO-DERIVATIVES

There are two main methods of preparing them: first, by the oxidation of amines, and secondly, by the reduction of nitro-compounds:—

$$C\text{–}NH_2 \longrightarrow C\text{–}N{:}O \;:\; C\text{–}NO_2 \longrightarrow C\text{–}N{:}O.$$

It was for a long time supposed that the nitroso-compound could only be obtained in these ways if there was no hydrogen attached to the same carbon as the NH_2 or NO_2. V. Meyer, in fact, laid it down as a general rule that nitroso-compounds containing the groups $-CH_2{\cdot}NO$ or $-CH{\cdot}NO$ could not exist, as they changed spontaneously into oximes $-CH{:}NOH$ or $=C{:}NOH$. We now know that there are some exceptions to this rule, which are of great interest. But it still holds good in the main. The majority of known nitroso-compounds are tertiary; these will therefore be dealt with first, and the exceptional cases of the secondary bodies later.

1. Oxidation of amines.

Bamberger has shown[1] that primary alkylamines, in which the NH_2 is attached to a tertiary carbon atom, such as tertiary butylamine $(CH_3)_3C{\cdot}NH_2$, when oxidized by Caro's acid (sulphomono-peracid) are converted into nitroso-derivatives:—

$$(CH_3)_3C{\cdot}NH_2 + 2\,O = (CH_3)_3C{\cdot}N{:}O + H_2O.$$

This nitroso-butane is the simplest nitroso-compound known, and it exhibits the characteristic properties of the group in a very marked degree. It forms colourless prisms, and is the most volatile solid known; this volatility is a very general characteristic of the nitroso-compounds. If it is exposed to the air for a short time it disappears entirely. If it is heated in an open tube it vanishes, without melting or boiling, when the temperature reaches 76°, and deposits in the cooler parts of the tube in the form of deep blue drops, which soon turn into a colourless crystalline solid. If heated in a sealed tube it melts at 76° to a deep blue oil. This of course means that under atmospheric pressure its boiling-point is lower than its melting-point; or, in other words, the vapour pressure of the solid becomes equal to one atmosphere at a temperature below the melting-point: hence it evaporates without melting. But when it is heated in a closed tube, the pressure produced by its own

[1] *Ber.* **36.** 685 (1903).

vapour raises the boiling-point without appreciably affecting the melting-point, till the boiling-point becomes higher than the melting-point, and the body melts. If an ethereal solution of nitroso-butane is distilled, the whole of it comes over with the ether vapour.

Nitroso-butane is easily soluble in organic solvents. The solutions are at first, like the solid, colourless; but they change gradually on standing, and rapidly on warming, to a deep blue. If the molecular weight of the dissolved substance is determined by the freezing-point method in the colourless solution, it is found to be twice that required by the simple formula $(CH_3)_3C{\cdot}NO$. But as the colour grows the molecular weight diminishes, until, when the colour has reached its deepest, it is only half what it was to begin with, and now corresponds to the simple formula. This, again, is a general characteristic of compounds containing a nitroso-group attached to carbon. It has long been known that such bodies when solid are colourless, and when melted or dissolved are blue or green. It has recently been shown that the coloured form always has the simple molecular weight, while the colourless form is a double polymer. In the case of nitroso-butane (and in many other instances) the solution of the colourless (bimolecular) solid is itself at first colourless and bimolecular. But on warming, or more slowly even at the ordinary temperature, the colourless double molecules break up into the blue simple molecules of C_4H_9NO. (Compare nitrogen peroxide, where the coloured NO_2 associates to the colourless double polymer N_2O_4.) It is a remarkable fact that this dissociation of nitroso-butane is delayed by exposure to sunlight. The colourless solution turns blue more rapidly in the dark. This associating action of sunlight has been compared to the behaviour of many unstable compounds, especially aldehydes, which polymerize much more rapidly in the light than in the dark.

By the same method Bamberger has obtained nitroso-isopropyl acetone by the oxidation of diacetone-amine, the product of the action of ammonia on acetone:—

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C\!<\!\begin{matrix} CH_2{\cdot}CO{\cdot}CH_3 \\ NH_2 \end{matrix} \longrightarrow \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C\!<\!\begin{matrix} CH_2{\cdot}CO{\cdot}CH_3 \\ N{:}O \end{matrix}.$$

This resembles nitroso-butane in its general properties, though it is less volatile. Its solution in organic solvents is colourless at first, but soon turns blue. It is curious that this dissociation occurs much less readily in water. The aqueous solution remains colourless for weeks, though it at once turns blue on warming. It is also worth noticing that in the case of this substance the monomolecular form is more stable than in nitroso-butane. Nitroso-isopropyl acetone—a colourless crystalline body, which must be the bimolecular form—melts at 75° to a blue (monomolecular) liquid, and if this is rapidly cooled it remains a blue liquid long enough for its properties to be examined, though it gradually changes into the colourless polymer. The white form is almost insoluble in cold organic solvents, and is not volatile. The blue unstable form is excessively soluble in organic solvents, and is volatile. Corresponding to this difference in volatility is the fact that whereas colourless solutions of this body have no smell, the blue solutions have a strong penetrating smell.

Triphenyl-methylamine $\phi_3C{\cdot}NH_2$ is not oxidized by Caro's acid at all. This may be due to stereo-chemical causes, and is at any rate to be remembered among the many peculiarities of the triphenyl-methyl compounds.

2. The second method of preparing fatty nitroso-compounds is by the reduction of the nitro-bodies. Those fatty hydrocarbons which contain a tertiary hydrogen atom readily give nitro-compounds on direct nitration, so that the tertiary nitroparaffins are comparatively easy to prepare. For example, di-isobutyl gives a nitro-compound of the formula $(CH_3)_2C\langle^{CH_2\cdot CH_2\cdot CH(CH_3)_2}_{NO_2}$, and Piloty has shown[1] that if this is treated with aluminium amalgam it is reduced to the β-hydroxylamine derivative

$$C{\cdot}NO_2 \longrightarrow C{\cdot}NHOH,$$

which, when oxidized with potassium bichromate, yields the nitroso-compound $(CH_3)_2C\langle^{CH_2\cdot CH_2\cdot CH(CH_3)_2}_{N:O}$. This is a colourless substance melting at 54° to a deep blue liquid, and resembling nitroso-butane in general properties.

3. A singular method of preparing a di-nitroso-compound of the fatty series is by the electrolysis of the sodium salt of the oxime of malonic ester[2]:—

$$2\,(CO_2Et)_2C{=}NO{\cdot}Na \longrightarrow \begin{matrix}(CO_2Et)_2C{-}N{:}O\\ |\\ (CO_2Et)_2C{-}N{:}O\end{matrix}.$$

The sodium goes to the cathode, while the residues liberated at the anode combine in pairs, as in Kolbe's electro-synthesis from the fatty acids. As the product is colourless, it is probable that the two nitroso-groups combine with one another.

4. Nitroso-compounds are formed by the action of nitrous fumes on the acyl derivatives of the fatty esters, especially when the acyl is attached to a tertiary carbon atom.[3] The acyl group is expelled and the nitroso takes its place, e. g.

$$\begin{matrix}CH_3{\cdot}CO{\cdot}CH{\cdot}CO_2Et\\ |\\ CH_2{\cdot}CO_2Et\end{matrix} \longrightarrow \begin{matrix}O{:}N{-}CH{\cdot}CO_2Et\\ |\\ CH_2{\cdot}CO_2Et\end{matrix}.$$

5. Piloty[4] has discovered a peculiar reaction of very general application, which gives rise to the halogen derivatives of the nitroso-compounds.[5] This consists in treating a ketoxime with bromine in the presence of pyridine. It is possible, though there is no evidence of this, that a hypobromite is formed as an intermediate product:—

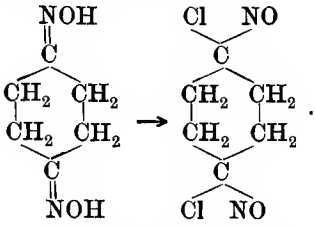
$$(CH_3)_2C{=}NOH + Br_2 = HBr + (CH_3)_2C{=}NOBr \longrightarrow (CH_3)_2C\langle^{Br}_{NO}.$$

The action of the pyridine is not understood. The product, brom-nitroso-propane, is a mobile blue liquid boiling at 83°, which has a strong smell resembling at once bromine and acrolein. It seems to have no tendency to form the colourless double polymer.

A remarkable example of the tendency of the NO group to polymerize is furnished by Piloty's chlor-nitroso-derivatives of diketo-hexamethylene.[6] The dioxime of para-diketo-hexamethylene (obtained from succino-succinic ester)

[1] *Ber.* **31**. 457 (1898). [2] Ulpiani, Rodano, *C.* **06**. i. 449.
[3] Schmidt, Widmann, *Ber.* **42**. 497, 1886 (1909). [4] *Ber.* **31**. 452 (1898).
[5] Cf. Ponzio, *C.* **06**. I. 1692. [6] *Ber.* **35**. 3101 (1902).

is converted by bromine and still more readily by chlorine into the corresponding di-halogen-dinitroso-derivative:—



This body is a blue crystalline substance, very soluble in organic solvents, melting at 108°. It changes slowly in alcohol, more rapidly in acetic acid containing hydrochloric acid, into a colourless crystalline substance of the same composition and the same molecular weight. This new isomer, when dissolved in methyl alcohol or acetone, gives a colourless solution which turns blue on heating, the colour disappearing again on cooling. The reactions of this isomer are in general similar to those of the original substance.

A consideration of the structure of the original body will show at once what the cause of this isomerism must be. This substance is obviously capable of the same stereoisomerism as hexahydro-terephthalic acid. The four valencies of the para-carbon atoms lie in one plane, and so two dichlor-dinitroso-derivatives can exist, a cis-trans, in which the two nitroso-groups are on opposite sides of the plane of the ring, and a cis, in which they are both on the same side. On the ordinary convention we can represent them on a plane thus:—

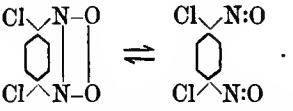


Cis-trans. Cis.

the essential point being that in the cis-form the two NO groups are near to one another, while in the cis-trans they are far apart. The blue crystalline body which is the product of the original reaction is clearly the cis-trans.

The two nitroso-groups are too far apart to combine with one another, and the body could only go into the colourless form by the combination of two molecules. But as is shown in the case of brom-nitroso-propane, which is a blue solid, there is less tendency to polymerization in these haloid derivatives than in the simple nitroso-compounds. Hence no such polymerization occurs. But when the body is allowed to stand in solution, it changes into the more stable cis-form. This is the colourless isomer. In this the two nitroso-groups are on the same side of the ring, and are therefore capable of combining. We thus get the two blue nitroso-groups changing into the colourless N_2O_2 within the molecule: and this is why the colour in this case disappears without an increase of molecular weight. That the product really has this formula is shown by the fact that its solution turns blue on heating. This cannot be due to the regeneration of the original cis-trans modification, because the blue colour immediately disappears on cooling, whereas the cis-trans only

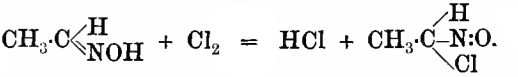
changes slowly into the cis. It must be caused by a separation of the two NO groups in the cis-form itself:—



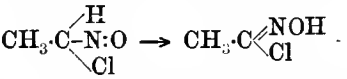
There is an obvious analogy between this case, where in one stereoisomer the two groups interact, while in the other they do not, and that of fumaric and maleic acids, where the cis-form (maleic acid) alone forms an anhydride.

The recently discovered secondary nitroso-compounds containing the group $=C\langle^{H}_{N:O}$ are obtained in two ways.

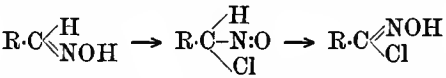
First, Piloty has shown[1] that acetaldoxime, when treated with chlorine, undergoes the same change as a ketoxime, giving a chlor-nitroso-compound:—



It is a colourless crystalline substance, which gives a colourless solution in liquid hydrocyanic acid at $-10°$, in which it is bimolecular. It melts at 65° to a deep blue liquid, and its solutions in organic solvents at the ordinary temperature are blue and monomolecular. If these solutions are warmed, or if the substance is kept fused for some time, the colour disappears, and the body is converted into the isomeric chloro-aldoxime, or hydroxamic acid chloride:—



Other aldoximes, such as benzaldoxime, do not give any such nitroso-compound. When they are treated with chlorine a transient green or blue colour is produced, showing that a nitroso-compound is formed, but this immediately vanishes, with the formation of the chloro-oxime. It is clear that the normal action of chlorine on an aldoxime is:—



In general the second reaction is so rapid that the nitroso-compound cannot be obtained; but in the particular case of acetaldoxime it is sufficiently slow to enable us to isolate the intermediate stage.

The second method of preparing the secondary nitroso-compounds is by the action of nitrous fumes on unsaturated hydrocarbons. But this will be discussed later,[2] in dealing with the rather complicated series of bodies to which this reaction gives rise.

The characteristic tendency of the nitroso-compounds to polymerization, with an accompanying loss of colour, a tendency which also occurs, as has been remarked, with the same accompaniment in the case of nitrogen peroxide, is not possessed by all the nitroso-bodies in an equal degree. On

[1] *Ber.* **35**. 3101 (1902). [2] p. 128.

the contrary, the relative stability of the mono- and bimolecular forms varies very greatly in different cases. We can arrange these compounds in a series[1] in the order of the increasing stability of the bimolecular form. In all cases the monomolecular form is characterized by being coloured and soluble in organic solvents, the bimolecular being colourless and much less soluble. At one end of the scale are certain cases, particularly of halogen derivatives, where the bimolecular form is so unstable that it cannot be obtained at all; thus brom-nitroso-propane (the acetone derivative) is a blue oil; and even the pinacoline derivative,

$$(CH_3)_3C{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}Br \quad ,$$
$$\qquad\qquad\quad \underset{\displaystyle N{:}O}{|}$$

which is solid, does not polymerize, but forms blue crystals. In the commoner cases the solid substance is the colourless form (as nitroso-butane), but on melting it turns blue.

The solutions are sometimes colourless below 0° (acetaldoxime compound), but blue at the ordinary temperature: in other cases they are colourless when freshly prepared, but turn blue on standing (nitroso-butane), while in cis-dichloro-dinitroso-hexamethylene the colourless form is so stable that the solution only goes blue on heating, and loses its colour immediately on cooling.

This brings us to a group of bodies, not hitherto mentioned, which were previously supposed to belong to a different class, but which obviously only continue the series of the nitroso-compounds. They are the so-called bis-nitrosyl-compounds. If benzyl-hydroxylamine, $\phi{\cdot}CH_2{\cdot}NHOH$, is oxidized[2] (which should produce a nitroso-compound), bis-nitrosyl-benzyl $\phi{\cdot}CH_2{\cdot}N_2O_2{\cdot}CH_2{\cdot}\phi$ is obtained. This is a colourless crystalline body which it is very difficult to break up at all, and hence it has been supposed that the N_2O_2 group must have some peculiar structure. It behaves, however, in other ways exactly like the colourless bimolecular nitroso-compounds; and by prolonged boiling with acetic and hydrochloric acids it can be split up into two molecules, when it gives not the true nitroso-derivative, but benzaldoxime. This, however, is to be expected. The vigorous action necessary to break up the firmly united N_2O_2 group is sufficient to change the very unstable primary nitroso-compound $\phi{\cdot}CH_2{\cdot}NO$ so formed into the isomeric benzaldoxime. In this body, too, the N_2O_2 group is stable enough to give some evidence as to its structure. We have hitherto assumed without any evidence that this is $\begin{matrix}-N-O\\ |\quad |\\ -N-O\end{matrix}$. The behaviour of bis-nitrosyl-benzyl indicates that the two nitrogen atoms are linked together, which is really all that is known about this grouping. For if the body is treated with hydrochloric acid in chloroform solution, it is converted into a mixture of benzoyl hydrazine, $\phi{\cdot}CO{\cdot}NH{\cdot}NH_2$, and benzoyl-benzal-hydrazine, $\phi{\cdot}CO{\cdot}NH{\cdot}N{:}CH\phi$. Hence the two nitrogens must be joined, and the body may be written

$$\phi{\cdot}CH_2{\cdot}\underset{\displaystyle O-O}{\overset{|\quad |}{N{-}N}}{\cdot}CH_2{\cdot}\phi \qquad \text{or} \qquad \phi{\cdot}CH_2{\cdot}\underset{\displaystyle O\ \ O}{\overset{\|\quad \|}{N{=}N}}{\cdot}CH_2{\cdot}\phi \ .$$

An example of a still more firmly united N_2O_2 group is afforded by

[1] Piloty, *Ber.* **35**. 3090 (1902). [2] Behrend, König, *Ann.* **263**. 212 (1891).

a class of compounds prepared by Baeyer, by treating certain terpene derivatives with nitrous acid. Thus from caron is obtained bis-nitrosyl-caron, $C_{10}H_{15}O{\cdot}N_2O_2{\cdot}C_{10}H_{15}O$. In this body the nitrogens are so firmly linked together that they cannot be separated at all. If the compound is broken up, it does not split between the nitrogen atoms, but between the N_2O_2 group and the carbon, losing one caron residue and giving $C_{10}H_{15}O{\cdot}N_2O_2{\cdot}H$.

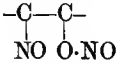
It follows from this gradation of properties that all the compounds dealt with belong to the same class, and that the stability of the N_2O_2 group increases by successive stages, though over a wide range.

We may consider here a group of substances whose formulae, reactions, and nomenclature are rather confusing; the nitrosites, pseudo-nitrosites, nitrosates, and the like, bodies obtained for the most part by the addition of the higher oxides of nitrogen (especially the trioxide and peroxide) to compounds with a double carbon link.[1]

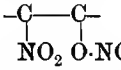
These nitrous vapours act as if they consisted of the trioxide, which adds itself on to the two doubly linked carbon atoms as $NO + NO_2$. Of these two groups the first must join directly through nitrogen to the carbon; the second may also do this, forming a nitro-group $C{-}NO_2$, or it may join through oxygen, forming a nitrous ester $C{-}O{\cdot}NO$; or this last may be the primary product, but may be oxidized further to a nitric ester $C{-}O{\cdot}NO_2$. We thus get the following groupings:—



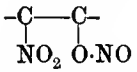
Pseudo-nitrosites.



Nitrosites.

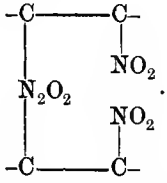


Wallach's Nitrosates.

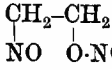


Gabriel's 'Dinitrüre', sometimes also called nitrosates.

The first two classes, being nitroso-compounds, may, and in fact generally do, occur in the bimolecular form, e. g.:—



Which of these bodies is obtained depends on the nature of the unsaturated compound employed. If the nitrous fumes act on a simple ethylene hydrocarbon,[2] or on a hydroaromatic compound, derivatives with the oxygen link (nitrous or nitric esters, nitrosites or nitrosates) are formed: e. g. with ethylene itself[3] the nitrosite



[1] See especially Wieland, *Ann.* **328.** 154; **329.** 225 (1903); Wieland, Bloch, *Ann.* **340.** 63 (1905).

[2] Wieland, *Ann.* **328.** 154.

[3] Schmidt, *Ber.* **35.** 2323 (1902).

The phenyl-ethylenes, especially those with positive substituents, such as anethol (*p*-methoxy-phenyl-ethylene), are able to attach both the nitrogen atoms to carbon directly, with the formation of pseudo-nitrosites, such as

$$\begin{array}{l} CH_3O\cdot C_6H_4\cdot CH\text{–}CH_2NO_2 \\ \qquad\qquad | \\ \qquad\quad N_2O_2 \\ \qquad\qquad | \\ CH_3O\cdot C_6H_4\cdot CH\text{–}CH_2\cdot NO_2 \end{array}.$$

With the accumulation of negative groups (especially if the other doubly linked carbon is joined to carbonyl, as in benzalacetophenone, $\phi\cdot CH{=}CH\cdot CO\cdot\phi$), though it is probable that these pseudo-nitrosites are the primary product, they become unstable, and the bodies actually obtained are either the nitro-oximes, $\begin{array}{l}\phi\cdot C\text{——}CH\cdot R \\ \quad | \qquad\quad | \\ \quad NOH\ NO_2\end{array}$, or their decomposition products, or unsaturated nitro-compounds, $\begin{array}{l}\phi\cdot CH{=}C\cdot R \\ \qquad\quad | \\ \qquad NO_2\end{array}$. At the same time a certain quantity of nitro-nitrous esters are formed, such as $\begin{array}{l}\phi\cdot CH\text{——}CH\cdot R \\ \quad | \qquad\quad | \\ \quad O\cdot NO\ NO_2\end{array}$.

The main distinction in these various groupings depends on whether the nitrogen is attached to carbon directly, or through oxygen. In the latter case (nitrosites or nitrosates) the nitrogen so attached is always removed with the greatest ease. Thus the true nitrosites, like that of ethylene, $\begin{array}{l}CH_2\text{—}CH_2 \\ | \qquad | \\ O\cdot NO\ NO\end{array}$, have the –O·NO group removed even by the action of alcohol. The nitrosates or 'Dinitrüre' split off the nitrous ester group even more easily, losing nitrous acid spontaneously, and thus passing into unsaturated nitro-ketones. The result of this is that where these nitrosates are formed by the action of nitrous fumes, there appears to be a direct nitration, the ketone being finally converted into a nitro-ketone, though in fact an addition product is first formed:—

$$\begin{array}{l}Ar\cdot CH{=}CH\cdot CO\cdot R \\ \quad + \ 2\ NO_2\end{array} \longrightarrow \begin{array}{l}Ar\cdot CH\text{——}CH\cdot CO\cdot R \\ \quad | \qquad\quad | \\ \quad O\cdot NO\ NO_2\end{array} \longrightarrow \begin{array}{l}Ar\cdot CH{=}C\cdot CO\cdot R \\ \qquad\quad | \\ \qquad NO_2\end{array} + HNO_2.$$

This suggests that similar intermediate addition products are formed in other cases of nitration as well.

The pseudo-nitrosites (also known as α-nitrosites) in which both nitrogen atoms are united to carbon, are more interesting. They are all bimolecular, owing to the polymerization of the nitroso-group; thus the styrol compound is:—

$$\begin{array}{l}\phi\text{–}CH\cdot CH_2\cdot NO_2 \\ \qquad | \\ \qquad N_2O_2 \\ \qquad | \\ \phi\text{–}CH\cdot CH_2\cdot NO_2\end{array}.$$

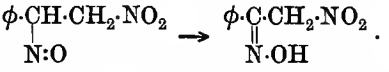
They are colourless crystalline compounds, very easily decomposed. They give green solutions in hot acetic acid, owing to the production of the monomolecular form, e. g.

$$\begin{array}{l}\phi\text{–}CH\cdot CH_2\cdot NO_2 \\ \qquad | \\ \qquad NO\end{array}.$$

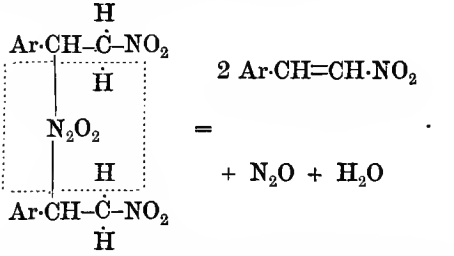
But on cooling, the solution loses its colour and deposits crystals of the bimolecular form.

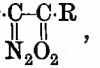
Their various decompositions all depend on two initial stages:—

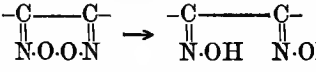
1. If they are boiled with alkali they first go into the monomolecular form, and then this, like all secondary nitroso-compounds in presence of alkali, changes over into the oxime:—



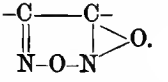
2. Under other conditions, especially in the presence of mineral acids, they split off the whole N_2O_2 group as hyponitrous acid (i. e. as nitrous oxide and water), and give unsaturated nitro-compounds:—



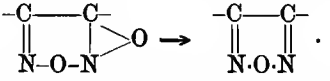
A remarkable reaction of the pseudo-nitrosites, which led to a misconception as to their structure, is their conversion into the so-called glyoxime peroxide. These 'peroxides' contain the group  , and as they are converted by reduction with zinc and acetic acid into the dioximes of α-diketones, they were formerly thought to have the two nitrogen atoms joined by a peroxide link:—



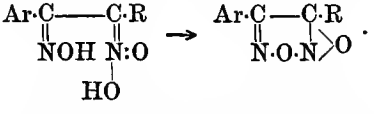
Later work,[1] however, has shown that they contain a 5-ring:—



Thus other reducing agents, such as tin and hydrochloric acid, convert them into furazane derivatives:—



Wieland has proved that the production of these peroxides from the pseudo-nitrosites takes place through the nitro-oximes (reaction (1) above), which yield peroxides if they are first dissolved in alkali (giving the aci-nitro-salt), and then the solution is acidified. This explains the mechanism of the reaction:—



Wieland, Semper, *Ann.* **358.** 36 (1908.)

But it is obvious that the nitro-oxime can exist in two stereoisomeric forms, and of these it is the anti-aryl form which will give the peroxide. Now, according to Hantzsch's investigations, the presence of positive substituents (such as methoxyl, $CH_3 \cdot O-$) on the aryl will favour this form, while their absence, or the presence of negative substituents, makes the syn-aryl form, which cannot undergo this change, the more stable. The facts bear out this view. If the aryl group of the pseudo-nitrosite contains positive substituents, the peroxide is formed at once, and the nitro-oxime cannot be isolated, whereas if these are absent, the nitro-oxime can be isolated, and is often quite a stable substance.

As has been pointed out, Wieland finds that the more negative bodies will often give no pseudo-nitrosites at all, but only the nitro-oximes. This probably means that the pseudo-nitrosites, which we may assume to be the primary products even in these cases, have less tendency to polymerize, and therefore undergo the normal change of the monomolecular nitro-secondary nitroso-compounds into the nitro-oxime.

AROMATIC NITROSO-COMPOUNDS

These, like the fatty derivatives, may be made either by the oxidation of amines or by the reduction of nitro-compounds. The simplest member of the group, nitrosobenzene, has long been known in solution. It was first prepared by Baeyer in 1874, by the action of nitrosyl bromide, NOBr, on mercury phenyl in benzene solution. But it was not isolated until nearly twenty years later. In 1893 Bamberger obtained it in the pure state by various methods: by the oxidation of diazobenzene with potassium ferricyanide or with potassium permanganate in alkaline solution, or better, by oxidizing β-phenyl hydroxylamine, ϕNHOH, with cold chromic acid mixture. This last is the method generally employed for preparing the aromatic nitroso-compounds. The nitro-compound is reduced, commonly with zinc dust and in neutral solution; this converts it first into the nitroso-compound and then into the β-hydroxylamine:—

$$Ar \cdot NO_2 \longrightarrow Ar \cdot NO \longrightarrow Ar \cdot NHOH,$$

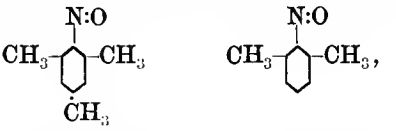
but the nitroso-group is so rapidly reduced further that it is practically impossible to stop the reaction at this stage. It is therefore allowed to go on another stage, giving the hydroxylamine derivative, and this is then oxidized back to the nitroso-compound. The nitroso-derivatives are so reactive that the experimental conditions, which differ somewhat in each case, must be very exactly observed.

The reduction can be effected electrolytically. Thus, if nitrobenzene is electrolysed[1] in neutral solution under suitable conditions, a good yield of nitrosobenzene is obtained. No diaphragm is used, and it seems that at the cathode the nitrobenzene is reduced to β-phenyl hydroxylamine, which is reoxidized at the anode to nitrosobenzene. Nitroso-compounds are also formed when an aromatic amine is oxidized with hydrogen peroxide or Caro's acid; but it is almost impossible in this case to isolate them.

[1] Dieffenbach, *C.* **08.** i. 911.

Nitrosobenzene can also be obtained by acting with nitrosyl chloride on phenyl magnesium bromide,[1] $\phi\cdot MgBr + NOCl = \phi\cdot NO + MgBrCl$.

The simplest and best known aromatic nitroso-derivative, nitrosobenzene, $\phi\cdot N{:}O$ (whose properties may be taken as typical of the whole class), forms large colourless crystals melting at 68° to an emerald green liquid. It is remarkable for being extraordinarily volatile—even to some extent with ether vapour. If its solution is distilled with steam, the whole of the nitroso-benzene comes over in the first few minutes. The same colour phenomena are observed with these bodies as with their fatty analogues; and the same changes in molecular weight have been found to accompany them, the substance being bimolecular in colourless solutions (where these can be obtained) and monomolecular when coloured. The aromatic nitroso-compounds show a great stability of the monomolecular form, the solutions being usually dissociated at the ordinary temperature. But it is to be noticed[2] that if there are two methyl groups in the ortho position to the –N:O, as in nitrosomesitylene and nitroso-meta-xylene,



the stereo-effect which they produce favours the stability of the bimolecular form: it promotes association. The solutions of these two bodies in organic solvents are of a very pale colour at the ordinary temperature, and contain mainly double molecules; they do not darken on standing but only on warming, and gradually lose their colour again on cooling.

The great reactivity of the nitroso-group indicates that it is under great strain; and this is further shown by the fact that if nitrosobenzene is ignited in oxygen under a pressure of 25 atmospheres it explodes.

Bamberger has examined the decomposition products formed under a variety of conditions in great detail: as an example of the scale on which he worked it may be mentioned that in a single set of experiments[3] on the action of alkali at 100°, 1,330 grams of nitrosobenzene were heated with alkali under pressure in 19 champagne bottles, and 12 different decomposition products were isolated and identified. Only the more important reactions of this substance can be dealt with here.

On reduction it yields first β-phenyl hydroxylamine and then aniline. When treated with hydrazobenzene, it oxidizes it quantitatively to azobenzene, being itself reduced to phenyl hydroxylamine:—

$$\phi\cdot N{:}O + \phi\cdot NH\cdot NH\cdot\phi = \phi NHOH + \phi\cdot N{=}N\cdot\phi.$$

On oxidation it is converted into nitrobenzene. With hydroxylamine it gives diazobenzene:—

$$\phi\cdot N{:}O + H_2NOH = \phi\cdot N{=}NOH + H_2O,$$

not, as originally stated by Bamberger, the anti, but the syn form.[4]

It combines with aniline to form azobenzene:—

$$\phi\cdot N{:}O + H_2N\phi = \phi\cdot N{=}N\cdot\phi + H_2O.$$

[1] Oddo, *Gaz.* **39.** i. 659 (1909).
[2] Bamberger, *Ber.* **34.** 3877 (1901).
[3] *Ber.* **33.** 1939.
[4] Hantzsch, *Ber.* **38.** 2056 (1905).

and with phenyl hydroxylamine very readily to give azoxybenzene :—

$$\phi\cdot N{:}O + \begin{matrix}HO\\H\end{matrix}\!\!>\!N\cdot\phi = \phi\cdot\overset{O}{\overset{\diagup\diagdown}{N}}\!-\!N\cdot\phi + H_2O.$$

It decomposes of itself in benzene solution if exposed to the light, giving mainly azoxybenzene, but also a variety of other products.[1]

The aromatic nitroso-derivatives which also contain an amine-group (the two nitrogen atoms being, of course, joined to different carbon atoms and not to one another) are obtained more easily by special methods.

Those with primary amine-groups are got from the nitrosophenols or quinone oximes (a class of bodies which will be described later) by heating them with ammonium chloride and ammonium acetate, the phenol hydroxyl being replaced by NH_2. Para-nitroso-aniline, $O{:}N\cdot\langle\bigcirc\rangle\cdot NH_2$, which is obtained in this way from benzoquinone monoxime (*p*-nitrosophenol),

$$O{:}N\cdot\langle\bigcirc\rangle\cdot OH + NH_3 = O{:}N\langle\bigcirc\rangle NH_2 + H_2O,$$

forms steel-blue needles. It gives salts with acids, which are yellow in solution, and also with potash. But if it is boiled with potash, the NH_2 is split off as ammonia, and the nitrosophenol regenerated.

The *p*-nitroso-derivatives of the secondary amines are got from the nitrosamines (in which the nitroso-group is attached to nitrogen) by the action of alcoholic hydrochloric acid, which causes the nitroso-group to migrate (in the normal manner) from the nitrogen to the para position on the ring :—

$$H\cdot\langle\bigcirc\rangle\cdot N\begin{matrix}CH_3\\N{:}O\end{matrix}\!\!> \rightarrow O{:}N\cdot\langle\bigcirc\rangle\cdot N\begin{matrix}CH_3\\H\end{matrix}\!\!>.$$

They are green crystalline substances, more basic than the primary compounds, which dissolve in alkalies and are reprecipitated by carbon dioxide. As secondary amines they react with nitrous acid to give the nitroso-nitrosamines, such as $O{:}N\cdot\langle\bigcirc\rangle\cdot N\begin{matrix}CH_3\\N{:}O\end{matrix}\!\!>$.

The corresponding derivatives of the tertiary amines are the best known of all the nitroso-compounds. They are formed directly with great ease by the action of nitrous acid on the tertiary amines. They are of commercial importance for the production of certain dyes, such as methylene blue and the indophenols.

Para-nitroso-dimethyl-aniline, $O{:}N\cdot\langle\bigcirc\rangle\cdot N\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>$, forms large green crystals. The stability of the monomolecular form is shown by the fact that the green colour does not perceptibly diminish if the toluene solution is cooled to below $-100°$ with liquid air. The hydrochloride is a yellow salt, and gives a deep yellow solution in water. On reduction it gives *p*-amino- and on oxidation *p*-nitro-dimethyl-aniline. On boiling with aqueous alkalies the amino-group is split off as dimethylamine, and nitrosophenol is formed.

A remarkable compound of this class is benznitrosolic acid,[2] $\phi\cdot C\begin{matrix}N{:}O\\NOH\end{matrix}\!\!>$, corresponding to the nitrolic acids $R\cdot C\begin{matrix}NO_2\\NOH\end{matrix}\!\!>$. It is obtained by the action

[1] Bamberger, *Ber.* **35**. 1606 (1902).

[2] Wieland, Bauer, *Ber.* **39**. 1480 (1906).

of potash on the benz-oxy-amidines, which first give a red azo-compound, and then break up to form the blue nitrosolic salt and an amidoxime :—

$$2\,\phi\cdot C\langle\begin{matrix}NHOH\\NOH\end{matrix} \longrightarrow \phi\cdot C\langle\begin{matrix}N{=}{=}N\\NOH\ HON\end{matrix}\rangle C\cdot\phi \;(-H_2O) = \phi\cdot C\langle\begin{matrix}N{:}O\\NOH\end{matrix} + \begin{matrix}H_2N\\HON\end{matrix}\rangle C\cdot\phi.$$

The total effect of these reactions is :—

$$2\,{-}NHOH = {-}NH_2 + {-}N{:}O + H_2O,$$

which may be compared to :—

$$2\,\phi\cdot CH{:}O \longrightarrow \phi\cdot CH_2OH + \phi\cdot CO\cdot OH.$$

Benznitrosolic acid forms an unstable green solution. It gives a red silver salt. It is easily reduced to an amidoxime ($-N{:}O \longrightarrow -NH_2$), and oxidized to a nitrolic acid ($-N{:}O \longrightarrow -NO_2$). When treated with mineral acids it forms benzonitrile and nitrous acid, the reaction no doubt being :—

$$\phi\cdot C\langle\begin{matrix}N{:}O\\NOH\end{matrix} + H_2O \longrightarrow HO\cdot NO + \phi\cdot C\langle\begin{matrix}H\\NOH\end{matrix} \longrightarrow \phi\cdot CN.$$

When the silver salt is treated with iodine, a quantitative yield of diphenyl-glyoxime peroxide is produced; this is no doubt due to the intermediate formation of the peroxide of the nitrosolic acid :—

$$2\,\phi\cdot C\langle\begin{matrix}N{:}O\\NOAg\end{matrix} + I_2 = \phi\cdot C\langle\begin{matrix}N{:}O\ O{:}N\\N\cdot O\cdot O\cdot N\end{matrix}\rangle C\cdot\phi + 2\,AgI \longrightarrow \begin{matrix}\phi\cdot C{-}{-}C\cdot\phi\\ |\quad\ |\\ N\cdot O\cdot N\quad O\end{matrix} + 2\,NO.$$

The simplest nitrosolic acid, methyl-nitrosolic acid, $H\cdot C\langle\begin{matrix}N{:}O\\NOH\end{matrix}$, has recently been obtained by Wieland and Hess,[1] by a method exactly analogous to that given above for the benzyl derivative : by the action of potash on form-oxy-amidoxime :—

$$2\,H\cdot C\langle\begin{matrix}NHOH\\NOH\end{matrix} \longrightarrow \left[H\cdot C\langle\begin{matrix}N{=}{=}N\\NOH\ HON\end{matrix}\rangle C\cdot H \longrightarrow\right] H\cdot C\langle\begin{matrix}N{:}O\\NOH\end{matrix} + \begin{matrix}H_2N\\HON\end{matrix}\rangle C\cdot H.$$

Its salts resemble those of the benzyl compound in colour, but they are more explosive. They are converted by the prolonged action of alkali into the salts of prussic and nitrous acids :—

$$H\cdot C\langle\begin{matrix}N{:}O\\NOH\end{matrix} = HCN + O{=}NOH.$$

The free acid is green in solution, but crystallizes in a yellow bimolecular form. It is very unstable, and decomposes into hyponitrous acid and fulminic acid :—

$$2\,H\cdot C\langle\begin{matrix}N{:}O\\NOH\end{matrix} = HON{=}NOH + 2\,C{=}NOH,$$

which is analogous to the change of methyl-nitrolic acid into fulminic and nitrous acids :—

$$H\cdot C\langle\begin{matrix}NO_2\\NOH\end{matrix} = HNO_2 + C{=}NOH.$$

As methyl-nitrosolic acid contains the secondary nitroso-group, $=C\langle\begin{matrix}N{:}O\\H\end{matrix}$, we should expect the hydrogen to migrate readily from the carbon to the nitroso-

[1] *Ber.* **42**. 4175 (1909).

group, which would give HON=C=NOH, the dioxime of carbon dioxide. This change cannot, however, be brought about at all, owing, probably, to the reluctance of the carbon atom to attach itself by two double links, which is shown also, for example, in the difficulty of forming hydrocarbons (allenes) of the type $H_2C{=}C{=}CR_2$.

QUINONE OXIMES OR NITROSOPHENOLS

When hydroxylamine acts on a quinone, a monoxime is formed, such as O:C$_6$H$_4$:NOH. These bodies are identical with the substances obtained by treating phenols with nitrous acid, and we should therefore expect them to be not oximes but nitrosophenols:—

$$HOC_6H_4{-}H + HO{\cdot}NO = HOC_6H_4{\cdot}N{:}O + H_2O.$$

This latter structure is also supported by the fact that they can be made by boiling the nitroso-tertiary aromatic amines with alkali, which replaces the amine-group by hydroxyl:—

$$(CH_3)_2N{\cdot}C_6H_4{\cdot}NO + H_2O = (CH_3)_2NH + HO{\cdot}C_6H_4{\cdot}NO.$$

The behaviour of these bodies is obviously tautomeric, and it is by no means easy to determine their real structure. The quinone oxime formula is supported by their production from quinone and hydroxylamine, and also by their conversion by the further action of hydroxylamine into the quinone dioximes, as HON=C$_6$H$_4$=NOH. Their formation from phenol and nitrous acid, and from nitroso-dimethyl-aniline, and (less certainly) their oxidation to nitrophenols, support the nitrosophenol structure. It is at least probable that their salts are derived from quinone oxime, for when the silver salt is treated with methyl iodide it gives an O-ether,[1] which must have the formula O:C$_6$H$_4$:NOCH$_3$, since it is also produced by the action of α-methyl hydroxylamine on quinone:—

$$O{:}C_6H_4{:}O + H_2N{\cdot}OCH_3 = O{:}C_6H_4{:}N{\cdot}OCH_3 + H_2O.$$

Moreover, the isomeric nitrosophenol ethers are also known,[2] being obtained by the oxidation of the aminophenol ethers with Caro's acid:—

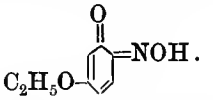
$$CH_3O{\cdot}C_6H_4{\cdot}NH_2 \rightarrow CH_3O{\cdot}C_6H_4{\cdot}N{:}O.$$

We may therefore conclude that the salts are derived from the quinone formula. It is commonly assumed that the free compound is also quinoid, but this is much more open to dispute. The argument from the colour, which is usually of great value in such cases, is here complicated by the tendency of the nitroso-group to polymerize to colourless compounds. Nitrosophenol[3] itself occurs in two crystalline forms, one colourless, the other brownish green. Its solutions in water, alcohol, and ether are green, and in ether it has been

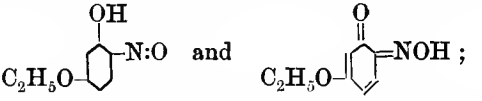
[1] Bridge, *Ann.* **277**. 79 (1893). [2] Baeyer, *Ber.* **35**. 3034 (1902).
[3] Sluiter, *Rec. Trav.* **25**. 8 (*C.* **06**. i. 756).

shown to be monomolecular. In benzene, chloroform, and carbon bisulphide it is yellow; in benzene its molecular weight is one and a half times that required by the simple formula. This behaviour is quite compatible with its being a nitroso-compound. There is also evidence that in forming the (probably quinoid) salts it undergoes an intramolecular change. It gives the ammonia reaction[1] which is characteristic of pseudo-acids, and the colour changes to yellow. This would seem to show that the free compound has a different structure from its salts, and hence is a nitrosophenol.

A case has recently been discovered[2] of a quinone oxime which is capable of existing in two very definite modifications, which there is strong reason to believe correspond to the two tautomeric formulae. If the monoethyl ether of resorcin is treated with nitrous acid, a body is produced whose formula, regarded as a quinone oxime, can be shown to be

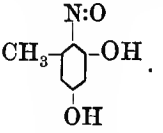


It is a golden-yellow crystalline solid, melting at 146°. If it is recrystallized from anhydrous non-ionizing solvents like benzene, toluene, or carbon bisulphide, it is converted into a green substance, strongly dichroic, and of a different crystalline form. The green form changes back into the yellow at 130°, or on recrystallizing from a dissociating solvent such as alcohol. The change seems to be brought about by the solvent at once. Solutions in benzene are always green, those in dissociating solvents yellow. Both forms give the same sodium salt when treated with soda, and the alkaline solution when acidified always precipitates the yellow modification. It is highly probable that these two forms correspond to the two tautomeric formulae,



and, further, that the unstable green form is the nitrosophenol (since green is the characteristic colour of the aromatic nitroso-compounds) and the stable yellow form the quinone oxime.

A somewhat similar case, but one which it is less easy to interpret, is that of nitroso-orcin.[3] This body, if it is to be considered as a nitrosophenol, has the structure



If its potassium salt is treated with acid below 0°, the free compound separates as yellow crystals, decomposing at 163°. If it is acidified when warm, red crystals are obtained, which change into the yellow form at 124–125°. The chemical behaviour of the two forms is the same, but they are not

[1] Farmer, Hantzsch, *Ber.* **32.** 3101 (1899). [2] Henrich, *C.* **04.** ii. 1539.
[3] Hantzsch, Sluiter, *Ber.* **39.** 162 (1906).

merely dimorphic, as the difference persists in solution (unlike nitroso-resorcin). The yellow form gives an orange-yellow solution in water, whose conductivity indicates a value of the dissociation constant K = 0·037. The red form gives a dark orange-red solution, of a higher conductivity, for which K = 0·051. If they are quite pure the two solutions remain unchanged for several days, but if not, their conductivities approach the same value. The addition of alcohol—even as little as 10 per cent.—brings about equilibrium from either side at once. If the solutions are evaporated *in vacuo* at the ordinary temperature they both leave the same mixture of the two solid forms; but if evaporated at 60–70° they both leave only the yellow form. The two forms give in all cases the same salt, even when treated with liquid ammonia at −70°. From the solution of the potassium salt acids precipitate at 0° the yellow form, at higher temperatures the red. The solution of the potassium salt at high dilution, when treated with an exact equivalent of hydrochloric acid, shows by its conductivity that it contains only the yellow form.

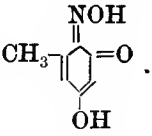
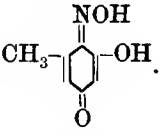
These two forms are obviously tautomeric, the yellow being less acidic than the red; and they change over into one another in solution in the usual way, the only remarkable fact being the unusually powerful catalytic influence of alcohol. But their stability relations are very difficult to explain. In the solid state the red form goes over into the yellow at 124°. Hence we should infer that the yellow is the stable form at high temperatures. On evaporating the aqueous solution at ordinary temperatures the mixture of the two forms is obtained: at higher temperatures the yellow alone. This again seems to show (though it is quite probable that equilibrium is not maintained throughout the whole process) that the yellow is more stable when hot. On the other hand, if the salt is precipitated with acid the red form is got at high temperatures and the yellow at low, which is just the reverse of what one would expect. The only explanation which seems possible is this. The form which is precipitated on acidification is produced rapidly, and so is not necessarily the stable modification; and it is conceivable that the potassium salt may also exist in two forms, and that the influence of temperature on their stability is the reverse of its influence on that of the free hydrogen compound; so that the potassium salt corresponding to the red form predominates in the solution when it is hot, and is therefore precipitated from such a solution by acids. But this seems improbable.

It is still less easy to assign formulae to the two modifications with any degree of probability. The body offers a great variety of tautomeric possibilities, since it has two unsymmetrically arranged hydroxyl groups, and since, further, besides the nitroso-oxime tautomerism,

$$(HO{\cdot}C\cdots C{-}N{:}O \longrightarrow O{=}C\cdots C{=}NOH),$$

you may have the ordinary keto-enolic change ($CH{=}C{\cdot}OH \longrightarrow CH_2{-}C{:}O$). Almost any of these formulae are equally compatible with the observed facts as to their tautomeric behaviour. It is worth noticing the suggestion

of Kehrmann [1] that both forms are monoketones (quinone oximes), but that the red is ortho-quinoid and the yellow para-quinoid:—

Red  . Yellow  .

We know that red and yellow are colours characteristic of the ortho- and para-quinones respectively, both in the simple benzoquinones and in many of their derivatives.

[1] *Ber.* **29**. 1417 (1899).

CHAPTER VII

NITRO-COMPOUNDS

The nitro-compounds are those in which the hydrogen attached to carbon is replaced by the group $-N\langle^{O}_{O}$. The aromatic nitro-compounds differ greatly from the fatty, mainly because they are necessarily tertiary. Many of the more important reactions of the primary and secondary fatty nitro-compounds are those in which the hydrogen atoms attached to the same carbon as the nitro-group take part; and these, of course, cannot occur with the aromatic derivatives. The two classes will therefore be dealt with separately.

FATTY NITRO-COMPOUNDS OR NITROPARAFFINS

The fatty nitro-derivatives were not discovered till long after the aromatic derivatives had become well known. They were first prepared by V. Meyer in 1872, and shortly afterwards by Kolbe.

The method of direct nitration, which is always used in the aromatic series, can only be employed with the paraffins in a limited number of cases. It is possible in several compounds which contain tertiary hydrogen (such as chloroform and isovaleric acid, $(CH_3)_2CH{\cdot}CH_2{\cdot}CH_2{\cdot}COOH$) to replace this tertiary hydrogen by NO_2 directly; and Konowalow has shown that direct nitration is also possible in the case of the normal hydrocarbons from hexane upwards. But it is remarkable that, whereas the method universally employed for nitrating the aromatic hydrocarbons is to use concentrated nitric acid in the presence of concentrated or even fuming sulphuric acid and to work at a low temperature (generally below 0°), Konowalow found, by an exhaustive series of experiments, that the most favourable conditions for nitrating the higher paraffins are to use dilute nitric acid, and to heat to a rather high temperature (130–140°). Nitric acid, of course, acts on organic compounds in two ways: it may nitrate them, or it may oxidize them. Both of these reactions are promoted by using a concentrated acid and by raising the temperature; and the extent to which these conditions can be employed in nitration is limited by the danger of oxidation. It would seem, therefore, that in the case of the aromatic hydrocarbons the influence of temperature on the nitration is less (or that of concentration is greater) than in that of the paraffins; and hence with the former we can use a low temperature and a very concentrated acid, while with the latter a high temperature is essential, and so to prevent oxidation the acid must be diluted.

In certain cases, however,[1] it has been found possible to apply the aromatic method to the paraffins as well, and by using fuming nitric acid to introduce,

[1] Poni, *C.* **02.** ii. 16.

for example, as many as three nitro-groups into isopentane, each group going to a different carbon atom; and recently Konowalow [1] has shown that where the hydrocarbon contains tertiary hydrogen atoms these are most readily replaced when a dilute acid is used, whereas if a stronger acid is employed the primary and secondary nitro-derivatives predominate.

The introduction of negative groups into the paraffins facilitates the formation of nitro-compounds. Thus, Konowalow [2] finds that by his method of using a dilute acid and a high temperature the chlorine derivatives of the hydrocarbons (such as butane and pentane) are more easily nitrated than the hydrocarbons themselves. So, too, acetic ester [3] can be directly nitrated at 30° by pure nitric acid in presence of acetic anhydride. If the negative groups are sufficiently powerful to produce an 'active methylene', as in malonic acid, nitration is still easier. Malonic ester [4] can be nitrated by concentrated nitric acid at the ordinary temperature, and its amide [5] even by somewhat diluted nitric acid without heating.

The more usual method of preparing the nitroparaffins is to heat the alkyl halides with silver nitrite:—

$$CH_3I + AgNO_2 = AgI + CH_3{\cdot}NO_2.$$

In this reaction the isomeric nitrites are formed as well as the nitroparaffins, in quantities depending on the nature of the alkyl halide employed. With methyl iodide, practically only the nitro-compound is formed, and this is the main product with primary halides containing up to 3 carbon atoms. But secondary halides, and any halides containing more than 4 carbon atoms, give very small yields of the nitro-compounds; while tertiary halides give almost entirely the nitrite. Mercurous nitrite behaves in the same way.[6]

Nitromethane may be prepared more easily by means of a reaction discovered by Kolbe. This consists in treating chloracetic acid with potassium nitrite. We may suppose that nitro-acetic acid is formed first, and that this at once splits off carbon dioxide to form nitromethane:—

$$\begin{matrix} CH_2Cl \\ | \\ COOH \end{matrix} \rightarrow \begin{matrix} CH_2{\cdot}NO_2 \\ | \\ COOH \end{matrix} \rightarrow CO_2 + CH_3{\cdot}NO_2.$$

A similar reaction is given [7] by the α-bromo-derivatives of propionic, butyric, and heptoic acids, which, when treated with potassium nitrite, give a 50 per cent. yield of the corresponding primary nitroparaffins. But if the α-bromine atom is attached to a tertiary carbon, the secondary nitroparaffin is not produced, but only a small quantity of the pseudo-nitrol:—

$$(CH_3)_2CBr{\cdot}COONa + 2\,NaNO_2 = (CH_3)_2C\begin{matrix} NO \\ NO_2 \end{matrix} + Na_2CO_3 + NaBr.$$

The nitroparaffins can be obtained from potassium nitrite still more easily by acting on its aqueous solution with ethyl hydrogen sulphate,[8] or better with the universal methylating agent, methyl sulphate.[9] In both cases a certain

[1] *C.* **06.** ii. 313
[2] *C.* **04.** i. 1478.
[3] Bouveault, Wahl, *C.* **04.** ii. 640.
[4] Ulpiani, *C.* **03.** ii. 343.
[5] Ratz, *Mon.* **25.** 55 (*C.* **04.** i. 1552).
[6] Rây, Neogi, *Proc. C. S.* **23.** 246 (1907).
[7] Auger, *Bull. Soc.* [3] **23.** 333 (*C.* **00.** i. 1263).
[8] Rây, Neogi, *J. C. S.* **1906.** 1900.
[9] Walden, *Ber.* **40.** 3214 (1907).

quantity of the isomeric nitrite is formed at the same time. These instances are worth noticing as being among the very few in which potassium nitrite acts as if its formula was $K{\cdot}N\ll^{O}_{O}$, its normal reactions corresponding to the structure K·O·NO.

A singular method of nitrating compounds which, like malonic ester, contain an acidic methylene group, is to act on them with ethyl nitrate and sodium ethylate ;[1] for example, with benzyl cyanide :—

$$NC\rangle^{\phi}CH_2 + Et{\cdot}NO_3 + NaOEt = NC\rangle^{\phi}CNO_2Na + 2\,EtOH.$$

If the product is boiled with soda,[2] it splits off the cyanide group as sodium carbonate and ammonia, and gives phenyl nitromethane, $\phi{\cdot}CH_2{\cdot}NO_2$. If this body, or the sodium salt of the original nitrile, is heated with soda to a high temperature, the nitro-group itself breaks off, and a good yield of stilbene is obtained. This reaction follows naturally from the formula for the salts of the nitroparaffins which will be established later:—

$$\phi{\cdot}\underset{CN}{\overset{|}{C}}{\cdot}NO{\cdot}ONa \longrightarrow \phi{\cdot}CH{\cdot}NO{\cdot}ONa \longrightarrow \phi{\cdot}CH{=}CH{\cdot}\phi.$$

It is remarkable that if tetraiodoethylene is treated with nitric acid it is converted into nitro-triiodoethylene, $CI_2{=}CINO_2$.[3]

The structure of the nitroparaffins is proved by their yielding primary amines on reduction. This shows that the nitrogen must be joined directly to carbon; if it was joined through oxygen it would split off on reduction to give an alcohol and a reduction product of nitrous acid, as happens with the isomeric nitrous esters.

The nitroparaffins are colourless liquids which are almost insoluble in water and distil unchanged. Their boiling-points are much higher than those of the isomeric nitrites, e.g. :—

Nitromethane ... B.Pt.	101°	Methyl nitrite....	−12°
Nitroethane.....	113°	Ethyl nitrite.....	+16°

Thus, they can easily be separated by distillation from the nitrites which are formed at the same time. Nitromethane is remarkable[4] for having a very high specific inductive capacity, but at the same time a very low ionizing power.

On reduction the nitroparaffins yield first β-hydroxylamines and then primary amines.

All nitroparaffins which still have hydrogen attached to the same carbon as the NO_2 are capable of dissolving in alkalies to form salts. Thus all simple primary and secondary nitroparaffins do so, but not the tertiary. Again, the primary compounds, such as nitroethane, $CH_3{\cdot}CH_2{\cdot}NO_2$, when their sodium salts are treated with bromine, give mono-bromo-derivatives, such as $CH_3{\cdot}CHBr{\cdot}NO_2$. This body can also give a sodium salt, and when the salt is

[1] W. Wislicenus, Endres, *Ber.* **35.** 1755 (1902); W. Wislicenus, Waldmüller, *Ber.* **41.** 3334 (1908).
[2] Wislicenus, Wren, *Ber.* **38.** 502 (1905).
[3] Biltz, Kedesdy, *Ber.* **33.** 2190 (1900); Nef, *Ann.* **298.** 346 (1897).
[4] Bruner, *Ber.* **36.** 3297 (1903).

treated with bromine another bromine atom is introduced, giving $CH_3{\cdot}CBr_2{\cdot}NO_2$. This substance is no longer capable of forming a sodium salt, because no hydrogen remains attached to the carbon. These bromine compounds are proved to have the halogen atom joined to carbon by their reaction with zinc ethyl: for example:—

$$\begin{matrix}CH_3{\cdot}CH{\cdot}NO_2\\ \quad\quad|\\ \quad\quad Br\end{matrix} + Zn(CH_3)_2 \rightarrow \begin{matrix}CH_3{\cdot}CH{\cdot}NO_2\\ \quad\quad|\\ \quad\quad CH_3\end{matrix}.$$

In the same way the mono-bromo-derivative of a secondary nitroparaffin, as $(CH_3)_2C\langle^{Br}_{NO_2}$, will not form salts with alkali.

These facts were discovered by V. Meyer, and he explained them by the very natural assumption that the presence of the strongly negative nitro-group renders the hydrogen attached to the same carbon atom (the α-carbon atom) acidic; but that this influence does not extend to the hydrogen attached to other carbon atoms in the same molecule: so that if all the α-hydrogen is replaced, the power of forming salts disappears. Subsequent researches have shown, however, that this explanation is not correct.

In the first place, Nef found that if the solution of the salt of a nitroparaffin is acidified, none of the nitroparaffin is regenerated, unless special precautions are observed. This in itself tends to show that the process does not consist merely in the replacement of the sodium by hydrogen; for if it did, the reaction should go quite easily. Moreover, the study of the decompositions which occur throws considerable light on the structure of the salt.

Before Nef's work V. Meyer had discovered that if the salt of a nitroparaffin was heated with acids, it broke up into an acid and hydroxylamine:—

$$CH_3{\cdot}CH_2{\cdot}NO_2 + H_2O = CH_3{\cdot}C\langle^{O}_{OH} + H_2NOH.$$

Nef finds that if the solution of the salt is added to dilute nitric acid at the ordinary temperature, no nitro-compound is regenerated; but practically the whole is split up into an aldehyde (or a ketone, if a secondary nitroparaffin is taken) and nitrous oxide. The formation of an aldehyde indicates that in the salt the nitrogen is joined to carbon by a double bond; and Nef suggests the following explanation. He assumes that the salt is derived from a tautomeric form of the nitro-compound and has the structure $CH_3{\cdot}CH{=}N\langle^{O}_{ONa}$. When this is treated with acid the sodium is first replaced by hydrogen, and then the product undergoes what he calls intramolecular oxidation:—

$$2\,CH_3{\cdot}CH{=}N\langle^{O}_{OH} = 2\,CH_3{\cdot}CHO + \begin{matrix}NOH\\ \|\\ NOH\end{matrix},$$

the hyponitrous acid breaking up at once into nitrous oxide and water.

The next advance was due to Holleman, who found that the colourless *m*-nitrophenyl-nitromethane, $\begin{matrix}C_6H_4{\cdot}CH_2{\cdot}NO_2\\ \quad\quad|\\ \quad\quad NO_2\end{matrix}$, gave a yellow sodium salt, and that when the solution of this salt was treated with an equivalent of hydrochloric acid, it at first remained yellow and had a higher conductivity

than that of the sodium chloride which it contained, indicating the presence of another electrolyte. But on standing the solution gradually lost its colour, and simultaneously the conductivity fell to that of the sodium chloride. This shows that the first effect of adding acid is to produce a coloured acid substance, which in time goes over into the colourless non-dissociated nitro-compound. Hence the salt must be derived not from the nitro-compound but from a tautomer.

Finally, Hantzsch succeeded in the case of phenyl nitromethane, $\phi\cdot CH_2\cdot NO_2$, and of its para-brom-derivative in isolating both the tautomeric forms. Phenyl nitromethane dissolves in soda to form a salt. If carbon dioxide is passed into the solution a yellow oil separates out slowly; but if the solution is treated with a mineral acid, a white crystalline precipitate forms at once. Both these substances have the composition of $\phi\cdot CH_2\cdot NO_2$; and Hantzsch has been able to show that the liquid precipitated by carbon dioxide is the true nitro-compound $\phi\cdot CH_2\cdot NO_2$, while the solid obtained with mineral acids is the tautomeric isonitro-derivative $\phi\cdot CH{=}N\langle^{O}_{OH}$. In the case of *p*-brom-phenyl-nitromethane both the isomers are solid. The true nitro-body, got as before by means of carbon dioxide, melts at 60°, while the isonitro-compound, produced with hydrochloric acid, melts at 89–90°.

The arguments by which these formulae are established are as follows:—

The solid form differs from the liquid in giving a reddish-brown colour with ferric chloride. This is a well-known test for hydroxyl, applied by W. Wislicenus in the case of the tautomeric formyl-phenyl-acetic esters.

Again, the solid reacts with phenyl isocyanate, a recognized test for hydroxyl, while the liquid does not. The reaction is indeed abnormal; the isocyanate takes up water from the nitro-compound, and is converted into diphenyl urea:—

$$2\ \phi\cdot N{=}C{=}O + H_2O = \begin{matrix}\phi\cdot NH\\ \phi\cdot NH\end{matrix}\!\!>C{:}O + CO_2;$$

but it is evident that a compound with hydroxyl attached to the nitrogen would lose water more easily than one without it. Further, the solid modification dissolves in alkali at once, while the liquid only does so on prolonged shaking. This is to be expected if the salt so produced is a direct derivative of the hydroxyl form (the solid), whereas the true nitro-compound (the liquid) cannot form a salt until it has undergone an intramolecular change.

Finally, the solid is a strong acid, which the liquid is not.

These facts show conclusively that the liquid is the true nitro-compound $\phi\cdot CH_2\cdot NO_2$, and the solid the hydroxylic isomer $\phi\cdot CH{=}N\langle^{O}_{OH}$.

Of the two, the liquid is the stable form, and the solid changes into it on standing, either in the pure state or in solution. The change can be followed by means of the ferric chloride reaction. In the pure state it is complete in a few days in the cold. In solution the velocity depends on the solvent. It is extraordinarily high in acetic acid; in water it takes about an hour at the ordinary temperature and four hours at 0°. In other solvents

it is slower, the order being: Water (greatest), alcohol, ether, benzene, chloroform (least), the order of the dissociating power and the dielectric constant, as in the case of formyl-phenyl-acetic ester.[1]

The nitroparaffins are typical instances of pseudo-acids. In fact it was in this connexion that Hantzsch developed the theory of pseudo-acidity. Pseudo-acids are a particular class of tautomeric substances distinguished by the fact that one form is much more acidic than the other. Hence a pseudo-acid exhibits all the characteristics of tautomeric substances. It changes reversibly into its isomer at the ordinary temperature, and is therefore capable of reacting according to both of the two isomeric formulae, being in fact in the liquid state a mixture of the two forms in equilibrium.

Pseudo-acids are distinguished from other tautomers by the marked difference in acidity between the two forms, from which it follows that one is much more highly dissociated than the other. This enables us to apply special means of investigation, in particular the reaction with indicators (or any other test for hydrogen ion) and the conductivity methods.

With the nitroparaffins, as with most pseudo-acids, the non-acidic form is the most stable in the free state. But this form is incapable of forming salts. Hence, if the free compound is treated with a base, the salt formed is derived from the other (acidic) modification: and when the solution of the salt is acidified it is the unstable acidic form which is first produced.

To return to the behaviour of the nitroparaffins in general. As has been stated, Nef showed that a solution of their salts when treated with acid gave an aldehyde and nitrous oxide; while V. Meyer found that, on heating with acid, a fatty acid and hydroxylamine were produced. This last reaction was explained by Bamberger,[2] who showed that when the salt is treated with acid, not only an aldehyde is produced, but also a hydroxamic acid, by a simple intramolecular rearrangement:—

$$R{\cdot}CH{=}N\begin{matrix}O\\OH\end{matrix} \longrightarrow R{\cdot}C\begin{matrix}OH\\NOH\end{matrix}.$$

If the salt is heated with acid, as in V. Meyer's experiment, the hydroxamic acid breaks up further, like any other oxime, giving hydroxylamine and the fatty acid:—

$$R{\cdot}C\begin{matrix}OH\\NOH\end{matrix} + H_2O = R{\cdot}C\begin{matrix}OH\\O\end{matrix} + H_2NOH_2.$$

Bamberger also finds that in this formation of hydroxamic acid from the isonitro-salt and acid, a transient blue colour is produced, indicating the production of a nitroso-compound. This is probably a nitroso-alcohol, which then changes, in accordance with the general tendency of secondary nitroso-compounds, into the hydroxamic acid:—

$$R{\cdot}CH{=}N\begin{matrix}O\\OH\end{matrix} \longrightarrow R{\cdot}C\begin{matrix}OH\\-N{:}O\\H\end{matrix} \longrightarrow R{\cdot}C\begin{matrix}OH\\NOH\end{matrix}.$$

With magnesium or zinc alkyl iodide, the nitroparaffins give secondary hydroxylamines[3]:—

$$R{\cdot}CH_2{\cdot}NO_2 + MgAlkI \longrightarrow R{\cdot}CH_2{\cdot}N\begin{matrix}OH\\Alk\end{matrix}.$$

[1] W. Wislicenus, *Ann.* **291**. 178 (1896). [2] *Ber.* **35**. 45 (1902). [3] Bewad, *Ber.* **40**. 3065 (1907).

If nitroethane is treated with mercuric chloride, a white salt,

$$CH_3{\cdot}CH{=}N\begin{matrix}O\\ O{\cdot}HgCl\end{matrix}'$$

is formed, which is not explosive. On the other hand, nitromethane gives with mercuric chloride a yellow salt, which explodes with the utmost violence. This remarkable difference in behaviour has been explained by Nef. He analysed the explosive nitromethane salt, and found it to be free from hydrogen. Further investigation showed it to be mercury fulminate. If we accept Nef's formula for the fulminates, which is practically certain, the reaction is easily accounted for. The first product is the mercuric salt of nitromethane; but this loses water by a kind of intramolecular oxidation:—

$$\begin{matrix}H_2C{=}N{\cdot}O{\cdot}hg\\ \|\\ O\end{matrix} = C{=}N{\cdot}O{\cdot}hg + h_2O\ (Hg = \tfrac{1}{2}\,Hg),$$

and this is Nef's formula for the fulminate. The reaction is a strong confirmation of Nef's views. It is obvious that no similar change is possible with the nitroethane salt.

Nitromethane condenses with benzaldehyde in presence of sodium ethylate. The primary product can be isolated, but it readily loses water to give ω-nitrostyrol:—

$$\phi{\cdot}CHO + CH_3{\cdot}NO_2 = \phi{\cdot}\begin{matrix}CH\\ |\\ OH\end{matrix}{\cdot}CH_2{\cdot}NO_2 \longrightarrow \phi{\cdot}CH{=}CH{\cdot}NO_2.$$

This reaction is strictly analogous to the aldol condensation:—

$$CH_3{\cdot}CHO + CH_3{\cdot}CHO = CH_3{\cdot}\begin{matrix}CH\\ |\\ OH\end{matrix}{\cdot}CH_2{\cdot}CHO \longrightarrow CH_3{\cdot}CH{=}CH{\cdot}CHO.$$

Among the substitution-products of the nitroparaffins the *α-nitro-ketones* are of some theoretical importance.[2] Having the nitro-group attached to the next carbon to the carbonyl they are analogous, in the enolic form, to the ortho-nitrophenols, as the grouping $-C(NO_2){=}C{\cdot}OH-$ occurs in both. They are also analogous in behaviour, giving three series of salts, (1) colourless, (2) yellow, (3) red. This difference of colour is not caused by water of crystallization, and so must be due to a difference of structure. Now the group $-CO{\cdot}CH{\cdot}NO_2-$ can change tautomerically into an acid form in two different ways, giving either (1) $C(OH){=}C{\cdot}NO_2$, or (2) $CO{\cdot}C{=}NO{\cdot}OH$. Both of these forms are colourless in their derivatives, as is shown for (2) by the colourless ester of dimethyl nitro-barbituric acid, which certainly has the group $=NO{\cdot}OAlk$; and for (1) by the colourless nitrophenol esters, such as $C_6H_4\begin{matrix}OCH_3\\ NO_2\end{matrix}$. Hence the colourless salts of the nitro-ketones must correspond to one or other of these two aci-forms.

In the coloured salts some further change must have taken place, and in two ways, one for the yellow and another for the red. This evidently implies the co-operation of the keto-group, as its presence is necessary to

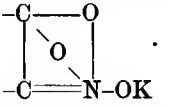
[1] Holleman, *Rec. Trav.* **23.** 298 (*C.* **05.** i. 89).

[2] Hantzsch, *Ber.* **40.** 1523 (1907).

the colour; but exactly how this takes place is uncertain. It is possible that the two forms are stereoisomers:—



or, more probably, they are structural isomers, one having one of the formulae given above, and the other some such structure as



The reactions of the nitroparaffins with nitrous acid are both of practical and of theoretical importance. They are closely analogous to those of the amines.

Primary nitro-compounds exchange the two hydrogen atoms for the oxime group, giving nitrolic acids:—

$$CH_3{\cdot}C\begin{cases}H_2\\NO_2\end{cases} + O{=}NOH = CH_3{\cdot}C\begin{cases}NOH\\NO_2\end{cases} + H_2O.$$

This is analogous to the formation of diazo-compounds from primary amines.

Secondary nitro-compounds exchange the one hydrogen for NO, giving nitroso-nitro-derivatives, or pseudo-nitrols:—

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C\begin{cases}H\\NO_2\end{cases} + HO{\cdot}NO = \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C\begin{cases}N{:}O\\NO_2\end{cases} + H_2O,$$

as secondary amines give nitrosamines.

Tertiary nitro-compounds, like tertiary amines, having no mobile hydrogen, do not react with nitrous acid at all.

The behaviour of the *Nitrolic Acids* is in many respects remarkable. Their structure is sufficiently established by the above method of formation, and by the fact that they can be made by treating the di-brom-substitution-product of a primary nitroparaffin with hydroxylamine:—

$$CH_3{\cdot}C\begin{cases}Br_2\\NO_2\end{cases} + H_2NOH = CH_3{\cdot}C\begin{cases}NOH\\NO_2\end{cases} + 2\ HBr.$$

But their salts show an isomerism not unlike that of the salts of the nitro-ketones. Hantzsch has shown,[1] for example, that ethyl nitrolic acid gives rise to three series of salts. It first produces very unstable colourless salts, which are probably the true nitrolates, as $CH_3{\cdot}C\begin{cases}NO_2\\NOK\end{cases}$. Their instability may well be due to their having the metal attached to the very weakly acid oxime-group, and in close proximity to the strongly acidic NO_2. They pass over with the greatest ease into the second series, which are bright red, and are known as erythro-salts: these are the usual product of the action of alkalies on the nitrolic acids, if no special precautions are taken. They regenerate the nitrolic acid when treated with acids. On heating, or on exposure to sunlight, these red salts change further into a third

[1] *Ber.* **31.** 2854 (1898); Hantzsch, Kanasirski, *Ber.* **42.** 889 (1909); Wieland, ib. 817.

series, which like the first are colourless, and which were originally termed leuco-salts. It is, however, more in accordance with analogy, as Hantzsch points out, to apply this term to the first series of (unstable) colourless salts, and to call the third series, which obviously are not true nitrolates at all, isonitrolates. These isonitrolates form the most stable series. They cannot be converted back into the red salts, and when treated with mineral acids they do not regenerate the nitrolic acid, but lose nitrous acid and form a polymer of the nitrile-oxide $CH_3 \cdot C\overset{O}{\diagdown\!\diagup}N$. In the same way on heating to 120° they break up into potassium nitrite and methyl isocyanate, $CH_3 \cdot N{=}C{=}O$, a product of the rearrangement of the nitrile-oxide. On reduction they give aldehydes. They can be shown to have the simple molecular weight. Hence the formula originally suggested by Hantzsch, $CH_3 \cdot C\begin{matrix}NO \\ NO \cdot OK\end{matrix}$, is excluded, as such a compound would be coloured owing to the nitroso-group. The most probable structure is

$$\begin{matrix}CH_3 \cdot C{=}N \\ KO \cdot N{-}O\end{matrix}\!\!>O.$$

Such a formula would account for their two chief decompositions: the compound would break up by itself along the dotted line, giving potassium nitrite and the nitrile-oxide; while on reduction hydrogen would add on to the double link, forming the imine $CH_3 \cdot CH{=}NH$ and then the aldehyde. The alternative formula,

$$CH_3 \cdot \overset{O}{\overset{\diagup\!\diagdown}{C}}\!\begin{matrix}N \\ |\\ O\end{matrix}, \qquad KO \cdot N{-}O$$

suggested by Wieland differs little from this: but the stability of the compound seems to point rather to a 5- than to a 4-ring.

The constitution of the red salts is uncertain; but it is evident that both the nitro- and the oxime-group take part in the salt formation; and we may write them $CH_3 \cdot C\begin{matrix}NO_2 \\ NO\end{matrix}\Big\}K$, on the analogy of the salts of the dinitroparaffins, $CH_3\begin{matrix}NO_2 \\ NO_2\end{matrix}\Big\}K$.

The *Pseudo-nitrols*, obtained by the action of nitrous acid on the secondary nitroparaffins, give the usual colour changes of the nitroso-compounds. If a solution of a secondary nitroparaffin is treated with nitrous acid, an intense blue colour is produced, but this soon disappears, while the colourless solid pseudo-nitrol separates out. If the solution is shaken with chloroform, the pseudo-nitrol is extracted by it, and the chloroform forms a deep blue layer at the bottom. This behaviour is strong evidence that the pseudo-nitrols contain the nitroso-group, and have the structure $R_2C\begin{matrix}NO \\ NO_2\end{matrix}$. This structure has been disputed, but it has been established beyond doubt by Piloty.[1] Piloty, as has been mentioned, obtained haloid nitroso-compounds by acting on the oximes with bromine; e. g. from acetoxime he prepared brom-nitroso-propane,

[1] *Ber.* **31.** 452 (1898).

$(CH_3)_2C\langle^{Br}_{NO}$. This body cannot have the isomeric formula $(CH_3)_2C{=}NOBr$, because the corresponding chlorine compound $(CH_3)_2C{=}NOCl$ is known (from the oxime and hypochlorous acid), and is a colourless pleasant smelling liquid of high boiling-point ; whereas the brom-nitroso-compound is a bright blue liquid of penetrating smell and low boiling-point. The latter must therefore be a true nitroso-derivative. Now when it is treated with silver nitrite[1] it is converted into isopropyl pseudo-nitrol, and this reaction can only take place in one way :—

$$(CH_3)_2C\langle^{Br}_{NO} + AgNO_2 = (CH_3)_2C\langle^{NO_2}_{NO} + AgBr,$$

so that the structure of the pseudo-nitrols is no longer open to doubt.

These bodies show the characteristic behaviour of nitroso-compounds in solution. At low temperatures the solution is colourless and the dissolved substance bimolecular ; at higher temperatures it turns blue, and the solute is now monomolecular.

The behaviour of the three classes of nitroparaffins with nitrous acid has been made use of by V. Meyer to distinguish primary, secondary, and tertiary alcohols. The alcohol is converted into iodide by treatment with phosphorus and iodine, and the iodide distilled with silver nitrite. This gives a mixture of nitro-compound and nitrous ester ; but the latter does not interfere with the reaction, and need not be removed. The product is shaken with a mixture of potassium nitrite and potash, and sulphuric acid slowly dropped in. If the original alcohol was primary, a red colour is produced (nitrolic salt), which disappears when the solution becomes acid, and comes back again if it is made alkaline. If it was secondary, a blue colour is formed, which disappears on standing, and on shaking with chloroform goes over into the latter. If it was tertiary, no colour appears at all.

This test can be used with all alcohols not containing more than five carbon atoms in the molecule, and does not require more than 0·3–0·5 gr. iodide.

POLY-NITROPARAFFINS

Of these the most important are those in which the nitro-groups are all attached to the same carbon atom. They may be obtained :

1. By oxidizing the pseudo-nitrols with chromic acid.

2. By the action of potassium nitrite on the mono-brom-mono-nitro-compounds :—

$$(CH_3)_2C\langle^{Br}_{NO_2} + KNO_2 = (CH_3)_2C\langle^{NO_2}_{NO_2} + KBr.$$

It is to be noticed that in this case potassium nitrite acts as a nitro-compound, and not as a nitrite.

3. By the action of concentrated nitric acid on ketones, which are thus broken up to form a dinitro-compound and an acid :—

$$2\,HNO_3 + C_2H_5{\cdot}CO{\cdot}C_2H_5 = C_2H_5{\cdot}C\langle^{H}_{NO_2}{}^{NO_2} + CH_3{\cdot}COOH + H_2O.$$

This reaction gives only the primary compounds.

[1] *Ber.* **35.** 3093 (1902).

The introduction of a second nitro-group greatly increases the tendency of the body to go over into the aci-form; and the primary dinitro-compounds are strong acids, existing in aqueous solution largely in the aci-form

$$R{\cdot}C\begin{matrix}NO_2\\ NO{\cdot}OH\end{matrix},$$

from which the salts are derived.

Their behaviour on reduction is remarkable. They easily split off one nitrogen to give an oxime, which on further reduction is converted into an amine[1]—

$$R{\cdot}CH(NO_2)_2 \longrightarrow R{\cdot}CH{:}NOH \longrightarrow R{\cdot}CH_2{\cdot}NH_2.$$

When heated with potash they give ammonia, potassium nitrite, and a fatty acid. It has been argued[2] from this looseness of attachment of the nitrogen, and especially from their behaviour on reduction, that both the nitrogen atoms cannot be attached to carbon, and the formula $R{\cdot}CH\begin{matrix}NO_2\\ O{\cdot}NO\end{matrix}$ has been suggested for them. As against this we have to observe that in the aci-form of the mono-nitro-compounds the nitrogen is easily split off (giving an aldehyde or ketone), as Nef showed, so that there is nothing surprising in the nitrogen being easily removed when there are two nitro-groups present. Moreover, now that the structure of the pseudo-nitrols is well established, their oxidation to dinitro-compounds makes it practically certain[3] that in the latter (at any rate in the secondary derivatives) both the nitrogen atoms are joined to carbon.

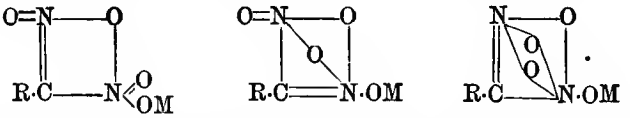
The salts of the dinitroparaffins have recently been investigated by Hantzsch.[4] As we have seen, the mono-nitroparaffins give colourless salts $R{\cdot}CH{=}N\begin{matrix}O\\ OM\end{matrix}$ (M = any monovalent metal), which are never known to occur in more than one form. The primary dinitroparaffins $R{\cdot}CH(NO_2)_2$ also give colourless salts, which no doubt have the analogous structure

$$R{\cdot}C\begin{matrix}NO_2\\ N{=}O\\ OM\end{matrix}.$$

But these are very unstable, and can only be obtained under special conditions. The ordinary salts are different, and belong to two series, one yellow and the other red (like the salts of the nitro-ketones and the nitrophenols). Which of these is obtained depends on the temperature, solvent, metal and anion, and it is only in a few cases that both forms have been isolated. They attain equilibrium in aqueous solution at once, the yellow form predominating at low temperatures and the red at high. In some cases the yellow can be crystallized from cold propyl alcohol, and the red from hot. They are monomolecular in water, and the conductivity of the solution is not affected by the change of colour; also the solid salts are anhydrous, so that the difference cannot be due to water of crystallization. Hence they must be isomeric. Dinitro-ethane is shown to be a pseudo-acid by the fact that it takes time to neutralize a base, and that the neutralization is accompanied by a correspondingly slow change of colour. The

[1] Ponzio, *C.* **02.** i. 976.
[2] Ponzio, *C.* **03.** i. 865.
[3] Scholl, *C.* **02.** ii. 937.
[4] *Ber.* **40.** 1533 (1907).

ordinary aci-form, $CH_3{\cdot}C\langle^{NO_2}_{NO{\cdot}OM}$, like the esters and salts of the mono-nitro-compounds, even when negatively substituted, as in $CH_3{\cdot}C\langle^{Br}_{NO{\cdot}OH}$ and $\phi{\cdot}C\langle^{CN}_{NO{\cdot}OH}$, would be colourless. Also the unstable colourless dinitro-salts obviously occupy this formula. It is clear that the change in structure is due to the tendency of the positive alkali metal to convert the anion of the salt into as negative a form as possible. How much is possible will depend on the nature of the compound: so that salts of different series will be obtained in different cases. As in the previous instances, the structure of the coloured salts is uncertain, but it is evident that both the nitro-groups must take part. Setting aside stereoisomerism, the following structures are possible:—



In the dinitro-compounds we have been considering, the two nitro-groups are symmetrically arranged with respect to the molecule. Where this is not the case, the number of isomers is doubled. This is realized in the salts of nitrophenyl-nitromethane $NO_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}NO_2$, where one nitro-group is on the nucleus, and the other on the side chain. In this compound, besides the colourless salt, which is unstable and no doubt has the normal iso-nitro formula $NO_2{\cdot}C_6H_4{\cdot}CH{=}NO{\cdot}OM$, there are no less than four series of coloured salts. Of these one is yellow and another red; from the similarity of colour to the salts of the dinitroparaffins, these must have the metal connected to the nitro-group in the side chain. Besides these, it is possible to prepare, usually by heating the solid red salt, a series of violet salts, which go over into a green series. These will obviously have the metal more closely related to the aromatic nitro-group. In the case of the potassium and caesium salts of the para compound, all four isomeric salts have been prepared, and three of them are known in several other cases. The colour does not depend on the degree of hydration, as this varies quite irregularly in the various series. The question of the structure of the nucleus in such cases will be discussed later, in dealing with the nitrophenols; but it may be noticed that the ortho and meta compounds have much less tendency to form these isomeric salts than the para, and the meta least.

Of the trinitroparaffins the only one of any importance is nitroform $CH(NO_2)_3$. It is obtained by a rather peculiar reaction from fulminuric acid, the isoamide of nitro-cyanacetic acid. If sodium fulminurate is treated with a mixture of concentrated nitric and sulphuric acids, it is converted into trinitro-acetonitrile:—

$$NC{\cdot}\overset{H}{\overset{|}{C}}{-}C\langle^{OH}_{NH} \rightarrow NC{\cdot}\overset{NO_2}{\overset{|}{C}}{-}NO_2,$$
$$\qquad\qquad\quad \dot{N}O_2 \qquad\qquad\quad \dot{N}O_2$$

and this can be made to take up water and form the ammonium salt of

trinitro-acetic acid, which however (like nitro-acetic acid) is unstable, and immediately loses carbon dioxide to give the ammonium salt of nitroform :—

$$(NO_2)_2{=}C\begin{matrix}NO_2\\ C{\equiv}N\end{matrix} + 2\,H_2O = (NO_2)_2{=}C\begin{matrix}NO_2\\ CO{\cdot}ONH_4\end{matrix}$$

$$= CO_2 + (NO_2)_2{=}C\begin{matrix}NO_2\\ NH_4\end{matrix} \rightarrow (NO_2)_2{=}C{=}N\begin{matrix}O\\ ONH_4\end{matrix}$$

Nitroform is a colourless liquid, which solidifies below 15°. Its solutions in non-ionizing solvents are also colourless. On the other hand, its aqueous solution and that of its salts are yellow. Further, in aqueous solution nitroform is a strong acid, almost wholly dissociated: while on the addition of concentrated hydrochloric acid (which must depress the dissociation) the colour becomes paler. This behaviour indicates that nitroform can exist in two tautomeric modifications: one colourless and undissociated, the other yellow and dissociated. The first (pseudo-acid) form is, no doubt, the true nitro-compound $HC(NO_2)_3$. The coloured acidic form was originally assumed by Hantzsch to be the iso-nitro-compound $(NO_2)_2C{=}NO{\cdot}OH$; but we now know that bodies of this type are, or at any rate can be, colourless, and it is more in accordance with the recent work on this class of compounds to suppose that in the coloured form a second nitro-group in some way takes part in the acidic structure.

The mercuric salt of nitroform[1] shows a very remarkable behaviour, to which there is scarcely any parallel. It is easily formed by dissolving mercuric oxide in nitroform, and is very soluble in many solvents, especially in ether, being even deliquescent in ether vapour. Unlike the other nitroform salts, which are yellow, the mercuric salt is colourless in the solid state, and so is its solution in ether, in benzene and its homologues, in ethyl acetate, ethyl oxalate, chloroform, carbon tetrachloride, and (still more remarkably) lactic acid. When dissolved in alcohols, fatty ketones, nitriles, chloracetic or acetic acids, it is pale yellow, while in water and in pyridine it is deep yellow. The depth of colour of equimolecular solutions ($N/_{32}$) in water, methyl alcohol, and ethyl alcohol is in the ratio 240 : 8 : 3. In other words, the mercuric salt has, roughly speaking, the same colour as free nitroform in the same solvent, while the potassium salt (and the other salts) is always yellow. Thus we have:—

	$CH(NO_2)_3$.	Hg salt.	K salt.
Pure substance	Colourless	Colourless	Yellow
Ethereal solution	Colourless	Colourless	(Insoluble)
Aqueous solution	Yellow	Yellow	Yellow

The mercuric salt is not associated in ethereal solution, for it gives the normal value of the molecular weight. We can only explain its behaviour in the same way as that of nitroform itself. The solid salt and its solutions in non-dissociating solvents must, like nitroform, contain three true nitro-groups, and therefore have the mercury attached to carbon $hg{-}C(NO_2)_3$; while the solution in ionizing solvents must have a tautomeric form, with the mercury attached in some way to oxygen. The mercury must migrate from

[1] Ley, Kissel, *Ber.* **32**. 1365 (1899); Ley, *Ber.* **38**. 973 (1905).

one position to the other, according to the solvent, just as the hydrogen does with a pseudo-acid, and hence mercuric nitroform should be called a pseudo-salt.

There is evidence that even in aqueous solution the compound is not wholly in the form of an oxygen salt. In the first place, the colour of the solution is paler than that of an equivalent ($N/_{32}$) solution of the potassium salt, in the proportion 1 : 3·6. Further, experience with other acids where no tautomeric change is possible, shows that the mercury salt of an acid is dissociated to about the same extent as the free acid itself. Now aci-nitroform (in aqueous solution) is about as strong an acid as trichloracetic. If therefore the mercuric salt in aqueous solution were present wholly as the O-salt, its dissociation should be about equal to that of mercury trichloracetate. It is found, however, to be much less, especially at high concentrations. This confirms the view that the aqueous solution of the mercuric compound contains a considerable percentage of the tautomeric undissociated form.

If silver nitroform is treated with methyl iodide, it gives the colourless stable trinitro-ethane $CH_3{\cdot}C(NO_2)_3$. Besides this we should expect, in view of the behaviour of other poly-nitroparaffins, that there would be at least one and possibly two isomeric forms of the alkyl derivatives. There is first the simple aci-form $(NO_2)_2C{=}NO{\cdot}OAlk$, which should be colourless, and secondly the coloured chromo-form of uncertain structure, where the second nitro-group comes into play. Hantzsch and Caldwell[1] have shown that, though no isomeric methyl nitroform can be isolated, there is reason to think that one is produced under certain circumstances. Silver nitroform gives an addition-compound with methyl iodide at $-70°$, of the composition $(NO_2)_2C(NO_2Ag)$, 2 CH_3I. If this is allowed to warm to the ordinary temperature either alone or in contact with anhydrous solvents, it changes explosively into trinitro-ethane; but if it is in contact with solvents containing water, it gives a quantitative yield of free nitroform. And yet, if silver nitroform is alkylated in water, alcohol, or ether, even at temperatures at which the addition-product gives only nitroform, it produces only traces of free nitroform, and an almost quantitative yield of trinitro-ethane. There seems to be only one possible explanation of these singular results. In solution (the last case) silver nitroform reacts in the form of ions. These can add the methyl group either to the carbon or to the oxygen. As the body formed by the former reaction (trinitro-ethane) is the more stable, it is the main product. But the solid addition-product reacts only in the undissociated form, by intramolecular change. The silver is attached to oxygen, and the methyl must therefore take its place on the oxygen. This gives the aci-ester, which is very unstable, and hence if water is present it is at once hydrolysed (like the corresponding aci-esters of the nitrophenols) to give free nitroform. If water is absent, it undergoes a further intramolecular change to give trinitro-ethane.

Hantzsch has recently drawn attention, in a short but extraordinarily ingenious paper,[2] to the unexpectedly close analogy between the corresponding derivatives of trinitro-methane and triphenyl-methane. Triphenyl-methane,

[1] *Ber.* **39.** 2472 (1906).

[2] *Ber.* **39.** 2478 (1906).

like trinitro-methane (nitroform), is easily prepared: but it is impossible to combine the two triphenyl-methyl groups into hexaphenyl-ethane $\phi_3C{\cdot}C\phi_3$; or if they can be so combined (for this is of course hotly disputed), at any rate they are so loosely held together that they separate with very unusual ease. To combine two trinitro-methyl groups into hexanitro-ethane $(NO_2)_3C{\cdot}C(NO_2)_3$ is quite impossible. The iodo-derivative of nitroform $(NO_2)_3C{\cdot}I$ will react readily with silver nitrite to give tetranitro-methane $C(NO_2)_4$, but it will not react with silver nitroform to give hexanitro-ethane at all. On the other hand, as tetranitro-methane is well known and quite stable, so is tetraphenyl-methane.

Again, the groups ϕ_3C- and $(NO_2)_3C-$ are remarkably similar in their 'Halochromie', that is, in their power of passing from a colourless undissociated form to a coloured salt: though the salt formation is less marked in the phenyl derivative, which is a weak base, and requires the presence of strong acids to bring about the change. The resemblance is shown in the following table:—

Colourless.	Coloured.
Pseudo-acid: $CH(NO_2)_3$	True acid: $C(NO_2)'_3 + H^{\cdot}$
Pseudo-base: $HO{\cdot}C\phi_3$	[True base: $HO' + C\phi^{\cdot}{}_3$]
Pseudo-salt: $hg{\cdot}C(NO_2)_3$	True salt: $C(NO_2)'_3 + hg^{\cdot}$
,, $Cl{\cdot}C\phi_3$	,, ,, $Cl' + C\phi_3^{\cdot}$

The last form may be supposed to occur in the coloured solution in sulphur dioxide, and in the coloured double chlorides. The question as to the structural change which is associated with the production of colour in the triphenyl-methane derivatives is very obscure, and cannot be discussed here: the most probable view with regard to the nitro-compounds (though this also is obscure) has already been mentioned. But the analogy between these two apparently remote groups of compounds is certainly worth noticing.

Tetranitro-methane $C(NO_2)_4$ is colourless and insoluble in water. It cannot form salts, as it has no hydrogen to be replaced; it is much more stable than nitroform, and can be distilled unchanged.

AROMATIC NITRO-COMPOUNDS

The aromatic nitro-compounds cannot be prepared by the action of silver nitrite on the haloid derivatives, as the halogen is too firmly attached to the nucleus. On the other hand, the method of direct nitration can be employed in this case with great effect, and this is of enormous importance, since the nitro-group can be exchanged, by means of the diazo reaction, for almost any other group.

This method was first used by Mitscherlich in 1834; he prepared nitro-benzene by acting on benzene with fuming nitric acid. It was soon discovered that an equally good yield may be obtained with much smaller quantities of nitric acid, if the nitration is carried out in presence of concentrated sulphuric acid, which takes up the water formed and causes the reaction to proceed to an end. The method which is now employed in the great majority of cases of nitration on the large scale, is to use the calculated quantity of nitric acid (an expensive substance from the technical point of view) mixed with excess

of concentrated or fuming sulphuric acid, and not to allow the temperature to rise above 0°. The reason for keeping the temperature low is that while this has comparatively little effect on the nitration, it enormously diminishes the oxidizing action of the nitric acid. The most striking example of this is that it is now found to be quite easy to nitrate aromatic aldehydes by working below 0°, without oxidizing the very sensitive aldehyde group to carboxyl.

In the laboratory the rather violent sulphuric acid is sometimes replaced by acetic anhydride: or if a milder nitrating agent is required, the compound may be dissolved in acetic acid and nitric acid run in. (In this way acetaldehyde can be nitrated at $-15°$.)

On the other hand, to make the poly-nitro-compounds, such as trinitrobenzene, a mixture of nitric and fuming sulphuric acids is used, and the reaction carried out at a high temperature.

The introduction of two nitro-groups into the nucleus is easy; but the introduction of a third is in most cases a matter of some difficulty; and in no case have more than three nitro-groups been put into the same nucleus.

The dynamics of the direct nitration of aromatic compounds have been investigated by Martinsen.[1] He used a solution of the aromatic compound and nitric acid in equivalent quantities (from half to tenth normal) in sulphuric acid. The progress of the reaction was measured by extracting the nitro-compound, or in some cases by determining the amount of free nitric acid remaining. He finds that the reaction is of the second order: that is, the velocity is proportional to the product of the concentrations of the nitric acid and the aromatic compound. Nitrous acid has no catalytic effect; but the strength of the sulphuric acid has a great influence on the velocity, which reaches a maximum for an acid of the composition H_2SO_4, $0{\cdot}7\ H_2O$, and falls off both towards the pure acid and towards the mono-hydrate. The amount of this influence varies with the nature of the substituent already present on the nucleus, being especially high in the case of the carboxylic and sulphonic acids. It is remarkable that where aqueous sulphuric acid is used, the addition of phosphorus pentoxide to this has no effect on the velocity.

The influence of substituents on the velocity of nitration is in the following order:—

$$NO_2 > SO_3H > CO_2H > Cl < CH_3 < O{\cdot}CH_3 < O{\cdot}C_2H_5 < OH,$$

where chlorine is put in the middle, since its effect is always small, and sometimes positive and sometimes negative: of the others, those to the left have an increasing effect in making the velocity less, and those to the right in making it greater. It is to be noticed that those substituents which diminish the velocity orient the nitro-group in the meta position, those which increase it in the ortho and para.

The immense increase in the facility of nitration produced by hydroxyl is indicated by the fact that phenol can be nitrated by dilute nitric acid in the cold.

If a homologue of benzene is heated with dilute nitric acid to a high

[1] *Z. Ph. Ch.* **50.** 385 (1905); **59.** 605 (1907).

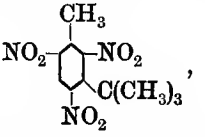
temperature, the nitro-group goes only into the side chain, toluene, for example, giving phenyl nitromethane, $\phi \cdot CH_2NO_2$. (The same thing occurs to some extent when it is nitrated in acetic acid solution.[1]) These are the conditions which are found to be most suitable for the direct nitration of the paraffins.

In comparison with the direct methods of preparing the aromatic nitro-compounds, the indirect are of scarcely any practical importance. But one or two are of sufficient theoretical interest to be worth mentioning. Aniline may be converted into nitrobenzene by oxidation, for example with sodium peroxide or potassium permanganate, and diazobenzene may be converted into it by treatment with potassium nitrite and cuprous oxide. To carry out this last reaction, which is due to Sandmeyer, the aniline is dissolved in excess of acid and diazotized by the equivalent quantity of potassium nitrite. As much more potassium nitrite is then added, and the solution of phenyl diazonium nitrite is poured on to moist freshly prepared cuprous oxide. An addition product of uncertain structure is produced, which breaks up into cuprous oxide, nitrogen, and nitrobenzene:—

$$\phi \cdot N_2 \cdot ONO \longrightarrow N_2 + \phi \cdot NO_2.$$

The mononitro-derivatives of the aromatic hydrocarbons are yellowish or colourless liquids or solids, which are nearly insoluble in water, but are easily soluble in strong nitric acid, from which they are precipitated on dilution. They are volatile in steam, and generally boil without decomposition. The polynitro-derivatives, on the other hand, if they are heated under atmospheric pressure, usually explode with more or less violence.

They often have strong and characteristic smells. That of nitrobenzene is scarcely to be distinguished from that of benzaldehyde; *p*-nitro-toluene has a smell resembling that of prussic acid; and trinitro-tertiary-butyl-toluene,



has an especially powerful odour, and is used in commerce as a scent, under the name of artificial musk.

The structure of these compounds, as true nitro-compounds with the nitrogen attached to carbon, is shown by the fact that they cannot be saponified as nitrites can (or only in particular cases and with difficulty), and that on reduction they are ultimately converted into primary amines.

The *reduction of nitro-compounds*, which has been examined in great detail, is by no means a simple process. A variety of products is obtained, according to the conditions of the reaction.

Speaking generally, the reduction proceeds in three ways, according as the solution is alkaline, neutral, or acid. In all cases the ultimate product, if the reducing agent is strong enough, is aniline. (For simplicity, the body

[1] Konowalow, Gurewitsch, *C.* 05. ii. 818.

reduced is assumed to be nitrobenzene: the presence of substituents does not seriously affect the results.)

If it is reduced in alkaline solution (with stannous oxide, alcoholic potash, &c.) the main products are those formed by the condensation of two molecules of nitrobenzene:—

$$\phi\cdot NO_2 + O_2N\cdot\phi \longrightarrow \phi\cdot N\!\!<\!\!\begin{matrix}\\O\end{matrix}\!\!>\!\!N\cdot\phi \longrightarrow \phi\cdot N{=}N\cdot\phi \longrightarrow \phi\cdot NH\cdot NH\cdot\phi.$$

Azoxy- Azo- Hydrazo-benzene

The earlier stages of the reduction proceed with great ease; it is sufficient to boil nitrobenzene with alkali in order to convert it into azoxybenzene; but for the further reduction of this a stronger reducing agent must be used. Where alcoholic potash or sodium methylate is used as the reducing agent, its action depends on the temperature employed.[1] At low temperatures the alcohol is oxidized to aldehyde, giving up two atoms of hydrogen. At higher temperatures sodium formate is produced: this implies that the alcohol takes up oxygen, but does not give off hydrogen:—

$$CH_3OH + 2\,O = H\cdot COOH + H_2O.$$

Hence at high temperatures the hydrogenized compounds, such as the hydrazo and the amine, are not produced, but only those compounds which are formed from the nitro by loss of oxygen alone, such as the azoxy and the azo.

Reduction in neutral solution leads, as has already been mentioned, to the β-hydroxylamine. It can be carried out by means of zinc dust or aluminium amalgam and water, and is promoted (for some reason not yet understood) by the presence of neutral salts, such as calcium or ammonium chloride. An unusual reducing agent which has been used for this purpose is red phosphorus and water.[2]

Reduction in acid solution leads normally to the formation of aniline; but under special conditions, particularly on electrolytic reduction, aminophenol is produced.

These are the main products of the reduction of aromatic nitro-compounds. It is obvious that such peculiar results call for some explanation; and in particular the formation of the bodies with two benzene nuclei—the azo-group—in alkaline solution, and practically only in alkaline solution, is most remarkable if it were not so familiar, and is clearly due to the interaction of the earlier reduction-products. The whole question has been investigated in great detail by Haber for the special case of electrolytic reduction, which is of great technical and also theoretical interest: and the conclusions which he has established there are applicable in the main to the chemical methods of reduction as well. The electrolytic method is peculiarly suitable for investigation. It can be carried on both in acid and in alkaline solution, and by varying the size of the electrodes and the current strength the reducing power can be altered to any required extent.

The electrolytic reduction of nitro-compounds is always a secondary process; that is to say, the nitro-compounds are not themselves electrolytes, and the reduction is entirely carried on by means of the hydrogen set free at the

[1] Rotarski, *C.* **05.** ii. 893.

[2] Weyl, *Ber.* **39.** 4340 (1906); **40.** 970 (1907).

cathode. We may consider that the electrolysis is a means of preparing on the surface of the cathode a solution of hydrogen, the concentration of which can be varied, as it depends on and is measured by the difference of potential between the cathode and the solution. It is only limited by the fact that at a certain concentration the hydrogen is given off at the cathode in bubbles; but even this limit can be altered by changing the material of the cathode.

We are thus able, by using the electrolytic method, to obtain the same variation of results as would be produced chemically by reducing agents of greater or less strength, and this without the complications which are necessarily introduced in the chemical method by changing the nature of the substances present: while the strength of the reducing solution of hydrogen can be determined from the cathode potential.

This last relation between the reducing power and the cathode potential is discussed in Haber's original paper[1]; the main results which he arrives at with respect to the reactions by which the various reduction-products are formed, and the order of their formation, are as follows.

The first established product of the reduction of an aromatic nitro-compound, whether in alkaline or in acid solution, is the nitroso-compound:—

$$\phi\cdot NO_2 \longrightarrow \phi\cdot NO.$$

There is, however, some reason to think that in certain cases there may be a stage intermediate between these two. Meisenheimer[2] has shown that para (and less easily ortho) dinitro-bodies can be made by careful reduction in alkaline solution to yield red (the ortho blue-violet) salts of the type $KO\cdot ON{=}\langle\!\rangle{=}NO\cdot OK$, which, when treated with acid, go over into the nitro-nitroso-derivative:—

$$C_6H_4\langle^{NO\cdot OH}_{NO\cdot OH} \longrightarrow C_6H_4\langle^{NO}_{NO_2}.$$

Their quinoid structure is supported by their colour, as ortho quinones are always darker than para. Meta-dinitro-compounds do not give derivatives of this kind. This initial stage is no doubt limited to those nitro-compounds which can easily go over into the quinoid form; but in such cases it seems probable that we begin with the three stages:—

$$-NO_2 \longrightarrow =NO\cdot OH \longrightarrow -NO.$$

But in general it may be assumed that the first reduction-product is under all circumstances the nitroso-compound. This, however, is much more rapidly reduced than the nitro-body, as is shown by the fact that a much lower cathode potential is sufficient for this purpose; so that it can never attain more than a very low concentration in the liquid. It has not been found possible to isolate it, but the fact of its formation has been established by the following experiment. If nitrobenzene is electrolysed in acid solution in the presence of hydroxylamine and α-naphthylamine, the well-known azo-dye benzene-azo-α-naphthylamine is produced. This dye is the result of coupling diazobenzene

[1] *Z. Ph. Ch.* **32.** 193 (1900).

[2] *Ber.* **36.** 4174 (1903); Meisenheimer, Patzig, *Ber.* **39.** 2526 (1906).

with α-naphthylamine, and it is clear that the diazobenzene must be formed by the action of the hydroxylamine on nitrosobenzene:—

$$\phi\cdot NO + H_2NOH = \phi\cdot N_2OH + H_2O,$$
$$\phi\cdot N_2OH + C_{10}H_7NH_2 = \phi\cdot N{=}N\cdot C_{10}H_6NH_2 + H_2O.$$

The nitrosobenzene, however, has only a transient existence, and is rapidly converted into the second reduction-product, β-phenyl-hydroxylamine, $\phi\cdot NHOH$. This, as has been shown, is a very reactive substance. In presence of acids it is converted into *p*-aminophenol, which consequently is a product of electrolytic reduction in acid but not in alkaline solution.

A reaction similar to this production of aminophenol takes place on reduction with a metal such as tin and hydrochloric acid,[1] when nitrobenzene gives a certain amount of ortho and para chlor-aniline: the hydroxylamine is no doubt converted by the hydrochloric acid into the chloramine, which then undergoes the usual change:—

$$C_6H_5\cdot N\langle{}^{OH}_{H} \rightarrow C_6H_5\cdot N\langle{}^{Cl}_{H} \rightarrow C_6H_4\langle{}^{NH_2}_{Cl}.$$

The yield of these bodies is increased by using a small quantity of the metal, which hinders the further reduction of the hydroxylamine, and by working at the boiling-point in presence of excess of hydrochloric acid, which promotes the intramolecular change.

The phenyl-hydroxylamine is also capable of other reactions. It condenses with the nitrosobenzene, the first reduction-product, to form azoxybenzene:—

$$\phi\cdot N{=}O + {}^{H}_{HO}\rangle N\cdot\phi = \phi\cdot N\underset{O}{\diagdown\!\!\diagup}N\cdot\phi + H_2O.$$

This reaction is of great importance, as it is almost the only source of all the 'bimolecular' reduction-products of the nitro-compounds, the azoxy-, azo-, and hydrazo-compounds, and hence the amounts of these bodies which are formed under any given circumstances of reduction—electrolytic or chemical—will depend on the velocity with which this reaction takes place. It is found that it proceeds very slowly in acid and much more rapidly in alkaline solution, and this explains why it is mainly in alkaline solution that the azo-group of compounds are obtained. The reason of this difference appears to be[2] that it is only the β-phenyl-hydroxylamine itself, $\phi\cdot NHOH$, which is able to undergo this condensation, and not its salts, $\phi\cdot NHOH\cdot HX$. Hence excess of acid delays the reaction by forming the salt; while it is found that the presence of negative substituents on the nucleus promotes it by increasing the hydrolysis.

The amount of azoxy-compound formed will obviously depend also on the concentration of the nitrosobenzene in the solution; and it is therefore diminished by working with a high current density, which reduces the nitroso-benzene to phenyl-hydroxylamine more rapidly, and consequently keeps its concentration down.

[1] Blanksma, *Rec. Trav.* **25**. 365 (*C.* **07**. i. 463).

[2] Flürscheim, Simon, *J. C. S.* **1908**. 1463.

There is another reaction, also occurring only in alkaline solution, which leads to the production of the azo-group of compounds ; and this is the conversion of the phenyl-hydroxylamine in presence of alkali into aniline and azoxybenzene :—

$$3\ \phi\cdot NHOH = \phi\cdot N(O)N\cdot\phi + \phi\cdot NH_2 + 2\ H_2O.$$

This affords another reason for the predominance of these derivatives in alkaline reduction.

Finally, the phenyl-hydroxylamine is also reduced electrolytically to aniline ; and in acid solution, where the coupling to azoxybenzene only occurs to a small extent, this is the chief source of the aniline which is the main product of the reduction.

But the list of reactions is not yet exhausted. We have seen how there are formed nitrosobenzene, phenyl-hydroxylamine, and azoxybenzene : as well as aminophenol and aniline, which do not react any further, and may therefore be set aside.

The azoxybenzene is further reduced by the electrolysis, not, as we might expect, to azobenzene, but directly to hydrazobenzene, which, however, never reaches more than a low concentration, as it undergoes in alkaline solution two, and in acid solution three, further changes. In acid solution, and there only, it is converted into semidine and benzidine :—

$$\phi\cdot NH\text{–}NH\cdot\phi \rightarrow H_2N\cdot C_6H_4\text{–}NH\cdot\phi \rightarrow H_2N\cdot C_6H_4\text{–}C_6H_4\cdot NH_2.$$

The semidine is to some extent oxidized by the nitrosobenzene to phenyl-quinone-diimide [1] :—

$$H_2N\cdot C_6H_4\text{–}NH\phi \rightarrow HN{=}C_6H_4{=}N\cdot\phi,$$

and this polymerizes to the dye emeraldine, of uncertain constitution, which has actually been obtained by electrolytic reduction in weakly acid solution under certain conditions.

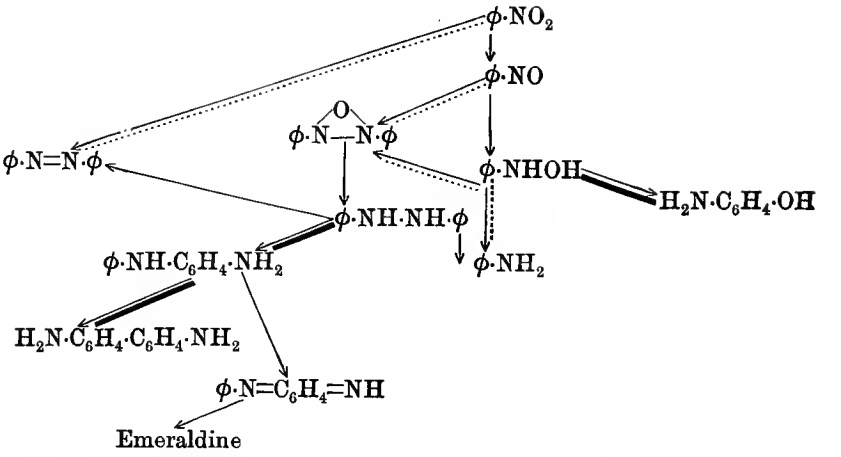
The second change undergone by the hydrazobenzene, both in acid and in alkaline solution, is its reduction to aniline.

The third change, which occurs in alkaline and to a small extent in acid solution, is that it is oxidized by the unreduced nitrobenzene to azobenzene. This is the source of the azobenzene which is formed in quantity in presence of alkali, and in traces in presence of acid :—

$$2\ \phi\cdot NO_2 + 3\ \phi\cdot NH\cdot NH\cdot\phi = 3\ H_2O + \phi\cdot N(O)N\cdot\phi + 3\ \phi\cdot N{=}N\cdot\phi.$$

These reactions are summarized in the following scheme. The vertical arrows indicate direct reduction by the electrolytic hydrogen, the oblique arrows chemical reactions. Those which occur only in acid solution are indicated by a thick line, those which occur chiefly in acid or alkaline solution are respectively distinguished by thick lines and dots.

[1] Nover, *Ber.* **40**. 288 (1907).



The important points to notice are these. The general scheme of the reduction is the same whether the solution is acid or alkaline; but the relative quantities of the various products are very different in the two cases. The chief difference arises through the behaviour of the phenyl-hydroxylamine. In acid solution it is rapidly reduced to aniline and very slowly condensed with nitrosobenzene to azoxybenzene. In alkaline solution it is only slowly reduced to aniline, while it is rapidly condensed to azoxybenzene (the starting-point of practically all the N_2 compounds) and is also converted into the same azoxybenzene (together with some aniline) by the direct action of the alkali, a reaction which does not occur in acid solution at all.

These facts explain the general results of the chemical reduction of nitro-benzene in acid alkaline and neutral solution respectively. They show why the main product in acid solution is aniline, and in alkaline solution one or other of the azo-group of bodies: while if phenyl-hydroxylamine is to be obtained, the solution must be neutral, because an acid converts it into amino-phenol, and an alkali promotes its condensation with nitrosobenzene to azoxybenzene and its change by spontaneous oxidation and reduction into azoxybenzene and aniline.[1]

The dynamics of the chemical reduction of nitro-compounds has been the subject of a series of investigations by Goldschmidt and his pupils.[2] The method used in all cases was to determine by titration from time to time the fall in the concentration of the reducing agent. Goldschmidt showed that in every case the reduction whose velocity is measured is that of the nitro to nitroso, the reduction of the latter to the hydroxylamine being infinitely rapid, and that of the hydroxylamine to the amine being always much quicker than the first stage, and sometimes too quick to be measured at all.

[1] For a fuller account of these phenomena see Möller, *Elektrochemische Reduktion der Nitrokörper* (Halle, 1903), and Haber's paper quoted above, together with his other papers in the *Zeitschr. f Elektrochemie*, especially 1897–8, p. 506.

[2] Goldschmidt, Ingebrechtsen, *Z. Ph. Ch.* **48**. 435 (1905); Goldschmidt, Sunde, ib. **56**. 1; Goldschmidt, Eckardt, ib. **56**. 385 (1906).

In the case of reduction by stannous halide in the presence of the haloid acid, he finds that with a constant concentration of the acid (say hydrochloric acid) the reaction is of the second order, the rate of reduction being proportional to the product of the concentrations of the nitro-compound and the stannous salt. If the concentration of the acid is altered, the velocity constant changes practically in the same proportion. It follows that the real reducing agent is not the stannous chloride, but the complex, $SnCl_3H$, or its ion, $SnCl_3$. It is probably the ion, since, if the hydrochloric acid is partly replaced by an equivalent of sodium chloride, the velocity is unchanged, which indicates that it is not the hydrogen ion which is important, but the chlorine ion.

If the stannous chloride and hydrochloric acid are replaced by stannous bromide and hydrobromic acid, the velocity constants for practically all the nitro-compounds examined become about eight times as large.

As regards the influence of the substituents in the nitrobenzene, it was found that if they are of a reactive character (such as COOH, NH_2), the velocity of reduction is greatest in the ortho compounds, and about the same in the meta and para. But a methyl group always diminishes the velocity, and to about the same extent whatever its position. This is remarkable, because the usual effect of a methyl group is to increase the reactivity of an organic compound, as in the velocity of diazotization and of nitration. *p*-Nitrophenol shows a peculiar behaviour, being reduced with great slowness by stannous halides, as it is by hydrogen sulphide. This is the more strange, as *p*-nitrosophenol (quinone oxime) is reduced instantaneously. The nitro-amines (as the nitranilines) occupy a peculiar position. Being weak bases, they are present in the acid solution partly as such, partly as the ions of their salts. It is found that the velocity of their reduction increases abnormally fast with increasing concentration of the acid. As the greater concentration of the acid increases the amount present in the ionic form (by diminishing the hydrolysis), it follows that the ion is reduced more rapidly than the free base. This view is confirmed by the fact that in these cases, and in these alone, the addition of sodium chloride, though it hastens the reduction, does not do so to the same extent as an equivalent quantity of hydrochloric acid. For though the chlorine ion increases the amount of the active reducing agent $SnCl_3$, the salt formation from the nitraniline is not increased by it, as it is by the hydrogen ion of the hydrochloric acid. The abnormal effect of hydrochloric acid was not observed in the case of the nitrophenols and the nitro-benzoic acids; from which Goldschmidt concludes that for these bodies the ion and the undissociated molecule have the same reduction velocities. But it is very doubtful whether this conclusion is justified. Such weak acids could hardly be expected to be dissociated to any appreciable extent in the presence of excess of hydrochloric acid.

In the case of reduction by an alkaline stannous solution Goldschmidt showed that such solutions contain the compound SnO_2HNa, and that the active agent is its ion SnO_2H'. Allowing for this, the reaction is again bimolecular, as required by the equation:—

$$R{\cdot}NO_2 + SnO_2H' = R{\cdot}NO + SnO_3H'.$$

The further stages of the reduction proceed, as in acid solution, with much greater velocity.

OXIDATION OF AMINES

This question has been postponed to this point because it is most easily understood in connexion with the reduction of the nitro-compounds. It has been worked out by Bamberger in a large number of cases in very great detail.[1] We may confine our attention to the primary amines, and disregard the less important oxidation products. The oxidizing agents used were commonly Caro's acid or hydrogen peroxide; in some cases also potassium permanganate and other substances. The precise agent employed has little effect on the course of the action, though it influences the proportion of the various products.

As has already been mentioned, when a tertiary amine is oxidized, it is converted into an amine-oxide, such as $\phi\cdot NMe_2{:}O$. Bamberger assumes that the same reaction occurs with a primary or secondary amine, but that in these cases, as there is also a hydrogen atom attached to the nitrogen, this body changes into the isomeric β-hydroxylamine:—

$$R\cdot N\langle{H\atop H} \longrightarrow R\cdot N(H)(=O) \longrightarrow R\cdot N\langle{H\atop OH}.$$

At any rate the first oxidation-product which can be detected, both with fatty and with aromatic amines, is the hydroxylamine derivative.[2] The nature of the further oxidation-products depends on whether the carbon attached to the nitrogen is primary, secondary, or tertiary. If it is tertiary, as with tertiary monobutylamine or aniline, the next stage is the formation of the nitroso-compound:—

$$C_3C\cdot NH_2 \longrightarrow C_3C\cdot N\langle{H\atop OH} \longrightarrow C_3C\cdot N{:}O.$$

The same thing may happen when the carbon is primary or secondary; but if so, the nitroso-compound cannot be isolated, going over at once into an aldoxime or ketoxime:—

$$\phi\cdot CH_2\cdot NH_2 \longrightarrow \phi\cdot CH_2\cdot NHOH \longrightarrow \phi\cdot CH_2\cdot N{:}O \longrightarrow \phi CH{:}NOH$$

$$(CH_3)_2CH\cdot NH_2 \longrightarrow (CH_3)_2CH\cdot NHOH \longrightarrow (CH_3)_2CH\cdot N{:}O \longrightarrow (CH_3)_2C{:}NOH.$$

If the oxidation is carried further, the ketoxime is converted into an isonitro-compound, which then changes into the normal nitro-compound:—

$$(CH_3)_2C{:}NOH \longrightarrow (CH_3)_2C{:}N\langle{O\atop OH} \longrightarrow (CH_3)_2CH\cdot NO_2.$$

[1] *Ber.* **31**. *1522* (1898); **32**. 342, 1675; **33**. *1781*; **34**. *2262*; **35**. 703, 714, 4293, 4299; **36**. *685*, *701*, 710, 817, 3827, 3831 (1903); *J. pr. Ch.* [2] **68**. 473, 480 (1903). The more important references are italicized.

[2] With a purely aromatic secondary amine, such as diphenylamine, it has been shown that a still earlier oxidation product is formed, the tetra-aryl-hydrazine,

$$2\phi_2NH \longrightarrow \phi_2N\cdot N\phi_2,$$

but this is easily broken up to give derivatives of the di-aryl-hydroxylamine ϕ_2NOH. Wieland, Gambarjan, *Ber.* **39**. 1499 (1906).

If the aldoxime (from an amine with primary carbon) is further oxidized, it is partly converted in the same way into an isonitro-, and so into a nitro-compound ; but some of it is converted into the hydroxamic acid.

The following schemes indicate the succession of reactions, the bodies not actually isolated being put in brackets.

Oxidation of a primary amine with primary carbon, such as benzylamine or ethylamine :—

$$\phi\cdot CH_2\cdot NH_2 \longrightarrow \left[\phi\cdot CH_2\cdot \underset{\underset{O}{\|}}{N}H_2\right] \longrightarrow \phi\cdot CH_2\cdot NHOH \longrightarrow \phi\cdot CH_2\cdot N{:}O$$

$$\longrightarrow \phi\cdot CH{:}NOH \begin{cases} \nearrow \phi\cdot C\langle {OH \atop NOH} \\ \searrow \phi\cdot CH{:}N\langle {O \atop OH} \end{cases} \longrightarrow \phi\cdot CH_2\cdot NO_2.$$

Oxidation of an amine with secondary carbon, as isopropylamine :—

$$(CH_3)_2CH\cdot NH_2 \longrightarrow \left[(CH_3)_2CH\cdot \underset{\underset{O}{\|}}{N}H_2\right] \longrightarrow (CH_3)_2CH\cdot NHOH \longrightarrow (CH_3)_2CH\cdot N{:}O$$

$$\longrightarrow (CH_3)_2C{:}NOH \longrightarrow ((CH_3)_2C{:}NOOH) \longrightarrow (CH_3)_2CH\cdot NO_2.$$

Oxidation of an amine with tertiary carbon, as tertiary butylamine :—

$$(CH_3)_3C\cdot NH_2 \longrightarrow \left[(CH_3)_3C\cdot \underset{\underset{O}{\|}}{N}H_2\right] \longrightarrow (CH_3)_3C\cdot NHOH$$

$$\longrightarrow (CH_3)_3C\cdot N{:}O \longrightarrow (CH_3)_3C\cdot NO_2.$$

The velocity of oxidation of amines by alkaline permanganate solution has been investigated by Vorländer,[1] though only in a qualitative way. He finds that a tertiary amine reacts more rapidly than a secondary, and a secondary than a primary ; and as regards the character of the radical attached to the nitrogen, a primary carbon atom gives the highest velocity, and a tertiary the lowest.

In the case of the aromatic amines, where the carbon is necessarily tertiary, the same series of oxidation products is obtained as with tertiary butylamine :—

$$-NH_2 \longrightarrow -NHOH \longrightarrow -NO \longrightarrow -NO_2.$$

But in this case a further series of reactions take place, which are impossible with the fatty compounds, the formation of aminophenols and of the bodies of the azo-group. These are in many respects the same as in the reduction of the aromatic nitro-compounds, the same original substances being present. The aminophenol is also oxidized to quinone, and the semidine (*p*-amino-diphenylamine), which is formed both from the hydrazobenzene and also by the action of the phenyl-hydroxylamine on the aniline[2] :—

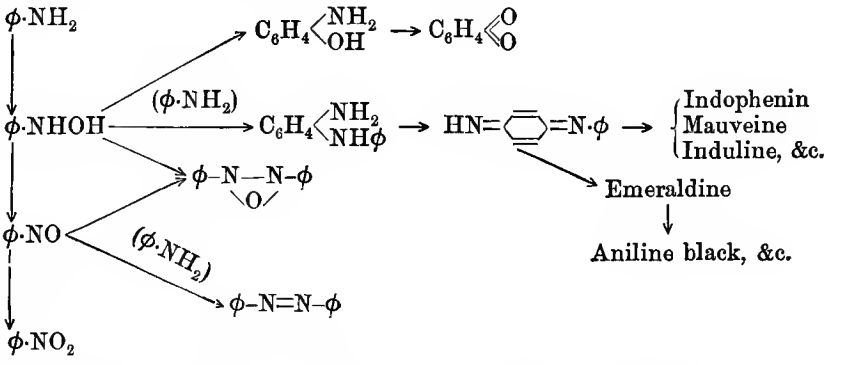
$$C_6H_5\cdot NHOH + H_2N\cdot\phi \longrightarrow C_6H_4\langle {NH_2 \atop NH\phi},$$

is oxidized to phenyl-quinone diimide, which is further converted[3] by a series

[1] *Ann.* **345**. 251 (1906). [2] *Ber.* **31**. 1522 (1898).

[3] Nover, *Ber.* **40**. 288 (1907). Cf. also Ostrogovich, Silbermann, *C.* **07**. i. 1194.

of complicated reactions into emeraldine, aniline black, and other dyes. The full scheme is as follows:—



To return from this digression to the reactions of the aromatic nitro-compounds.

The nitro-groups may be exchanged indirectly for almost any others by reducing them to NH_2 and diazotizing. But a direct exchange is difficult, especially in the case of the simple mono-nitro-derivatives. If there are several nitro-groups present it can be effected more easily. Thus ortho and para, but not meta, dinitrobenzene can have the NO_2 replaced by OH (with the formation of potassium nitrite) on boiling with potash; by ethoxyl (OC_2H_5) on treatment with alcoholic potash; and by NH_2 or $NH\phi$ with ammonia or aniline. This is only one of the many instances which show that the effect of one substituent on another is much greater in the ortho or para than in the meta position. There are other similar cases among the haloid nitro-compounds. If more than two nitro-groups are present, these exchanges can occur even when they are in the meta position, as in symmetrical trinitrobenzene.

The presence of nitro-groups also exerts a great influence on the behaviour of other substituents in the molecule. For example, the hydrogens attached to the nucleus are more easily oxidized. Nitrobenzene, when heated with solid potash, is converted into nitrophenol, while poly-nitro-compounds can be oxidized to phenols with potassium ferricyanide. In the same way the link between chlorine and the nucleus is very much weakened in the haloid nitro-derivatives.

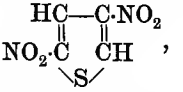
The poly-nitro-derivatives of the aromatic hydrocarbons show in some respects a peculiar behaviour. They have the power, which is shared by some of their substitution-products, such as picric acid, of combining to form crystalline addition-products with aromatic hydrocarbons like benzene, naphthalene, and anthracene (but generally not with the homologues of these hydrocarbons). Thus symmetrical trinitrobenzene gives a compound with benzene of the composition $C_6H_3(NO_2)_3 \cdot C_6H_6$. These are, however, unstable compounds, which readily give up the hydrocarbon again.

More stable addition-compounds are formed with amines[1] in particular

[1] Hepp, *Ann.* **215.** 344 (1882); Reverdin, Crepieux, *Ber.* **33.** 2507 (1900); Sudborough, *J. C. S.*

by symmetrical trinitrobenzene. These are coloured bodies, which can generally be recrystallized unchanged, and in some cases the amino-group can even be acetylated without breaking up the compound. No satisfactory formula has been proposed for these compounds, but they are probably analogous to the alkaline derivatives described below.

The behaviour of the nitro-compounds with alkalies is very remarkable. Mono-nitro-derivatives, such as nitrobenzene, are not affected by alkalies in the cold. It is true that ordinary commercial nitrobenzene, if dissolved in alcohol and treated with a drop of potash solution, gives a red colour. But this is due to the presence of dinitrothiophene,

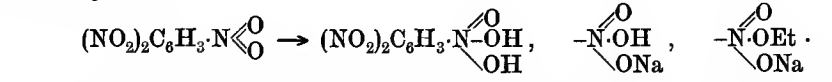


which is formed from the thiophene in the original benzene. Pure nitrobenzene gives no such colour.[1]

But the di- and tri-nitro-derivatives, even when pure, give colours with alkali. Thus *s*-trinitrobenzene gives a red colour with alkali, and trinitromesitylene dissolves in potash, forming a red solution. These phenomena point clearly to the formation of salts; and V. Meyer[2] supposed that the presence of the nitro-group rendered the hydrogen attached to the nucleus acidic, and that in the red compound produced by treatment with potash this hydrogen was replaced by potassium.

Lobry de Bruyn[3] has, however, shown that this explanation cannot be correct, since metallic potassium does not react with trinitrobenzene. He also succeeded in isolating one of these compounds. If a solution of trinitrobenzene in methyl alcohol is treated with a molecular proportion of potash in concentrated aqueous solution, red crystals separate out, whose composition is expressed by the formula $[C_6H_3(NO_2)_3CH_3OK]_2 \cdot H_2O$. They are explosive, and on treatment with acids regenerate trinitrobenzene.

The subject has been further investigated by Hantzsch,[4] who has isolated several of these compounds and has discussed their constitution. Since they are formed by direct addition, and not by replacement of the hydrogen, he first assumed that the addition must take place to the nitro-group alone, in this way:—



Subsequently, however, it was urged by Meisenheimer[5] that though this structure will explain many of the reactions of the compounds it wholly fails

1901. 522; Hibbert, Sudborough, ib. **1903**. 1334; Sudborough, Picton, ib. **1906**. 583; Noelting, Sommerhoff, *Ber.* **39**. 76 (1906); Kremann, *Mon.* **25**. 1215; *C.* **05**. i. 161, 162.

[1] This reaction can be employed to test benzene for its thiophene, its most common impurity. A few c.c. of benzene are warmed in a test tube with a mixture of nitric and sulphuric acids, and the product is poured into water and washed. It is then dissolved in alcohol and a drop of concentrated potash solution added. If the benzene was free from thiophene, the liquid remains colourless; if not, it turns red.

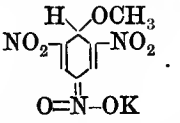
[2] *Ber.* **27**. 3153 (1894).

[3] *Rec. Trav.* **14**. 89 (1895).

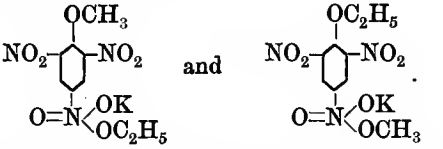
[4] Hantzsch, Kissel, *Ber.* **32**. 3137 (1899).

[5] *Ann.* **323**. 219 (1902).

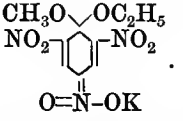
to account for their colour. He therefore suggested that the alkoxy-group was attached not to the nitrogen but to the para carbon atom of the benzene ring, e. g.



This point he was able to establish in an ingenious way. If we combine on the one hand trinitroanisol with potassium ethylate, and on the other trinitrophenetol with potassium methylate, the products on Hantzsch's theory will be different, having the formulae

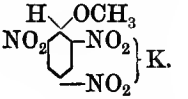


On Meisenheimer's view the alkoxy-group attaches itself to one of the three carbons which are in the para position to nitro-groups: i. e. either to one of the CH groups or to the C·OCH_3. If it should happen to be the latter, then the structure of the product will be the same in both cases, namely

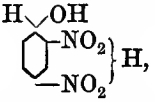


Experiment showed that the products of the two reactions were in fact identical, so that it is certain that the alkoxy-group is attached to the para carbon and not to the nitrogen.

In a more recent paper Hantzsch[1] has pointed out that while these results are conclusive as far as they go, Meisenheimer's formula still fails to account for the colour, since we know that both quinols and iso-nitro-salts are colourless. It is evident that the colour depends in some way on the co-operation of a second nitro-group, and therefore the formulae must be written (on the analogy of the other coloured nitro-derivatives)



Hantzsch has isolated several of these bodies, and also prepared derivatives of them. The mother substance of the whole group is a body of the structure

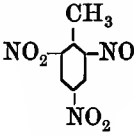


for which we may retain Hantzsch's name of nitronic acid.

Among the aromatic compounds the formation of derivatives of the nitronic acids does not occur with the mono-nitro bodies, and only with some of the

[1] Hantzsch, Picton, *Ber.* **42**, 2119 (1909).

di-nitro; it is most marked with the symmetrical tri-nitro-derivatives, the stablest compounds being those obtained from symmetrical trinitrotoluene,

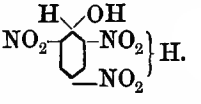


In this case both the ester salt and the free ester acid can be isolated, and are comparatively stable substances.

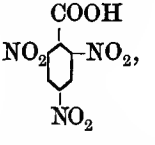
The ester salt $(CH_3)(NO_2)_2{-}C_6H_2{=}N{\cdot}OK$ is got by treating the nitro-compound with potassium methylate in methyl alcohol solution. It forms dark violet crystals which explode violently on heating. Measurements of electrical conductivity show that it is considerably hydrolysed in water. If its solution in dilute methyl alcohol is treated with an equivalent of hydrochloric acid at $-5°$, the free ester acid $(CH_3)(NO_2)_2{-}C_6H_2{=}N{-}OH$ is obtained as a dark red precipitate, also explosive, which is very slightly soluble in water, ether, and benzene, but more so in acetic acid. A determination of its molecular weight by the freezing-point of its acetic acid solution gave results agreeing with the formula. Its electrical conductivity shows it to be a weak acid. It is remarkable that it is not acted on by phosphorus pentachloride, but with acetyl chloride it gives the corresponding acetate.

Hantzsch was unable to isolate either the free nitronic acids or their salts; but he obtained evidence of the existence of both classes of compounds in solution.

The conductivity of a solution of *s*-trinitrobenzene in soda is found to be rather less than that of the original soda solution (e. g. $\mu=113{\cdot}5$ instead of 125). This shows that a small amount of combination has taken place, as indeed is evident from the red colour of the solution. When the solution is treated with acids the colour remains, and the conductivity is found to be seven units higher than that of the sodium chloride which the solution contains, so that it is evident that there is present in the solution a small quantity of the free nitronic acid,

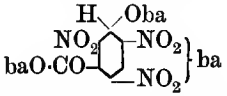


The nitronic salts can be isolated in the case of *s*-trinitrobenzoic acid,



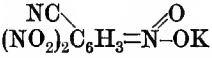
a body whose behaviour is interesting in several ways. It is colourless, and if its dilute ($N/_{32}$) solution is treated with one equivalent of soda, a colourless solution of the ordinary benzoate is obtained. The further addition of soda produces a deep red coloration, showing that a nitronic salt is formed. If a whole second equivalent of soda is added, the conductivity of the solution

is found to be 220; whereas the sum of the conductivities for $N/_{32}$ solutions of the simple sodium salt and sodium hydrate is 282. This indicates that the second molecule of soda has largely though not wholly combined; or in other words, that the nitronic salt is formed, but is to a considerable extent hydrolysed. That the solution does contain a di-sodium salt is shown by its giving precipitates with the solutions of the salts of the heavy metals, such as lead and silver. If the acid is neutralized with baryta instead of soda, the very slightly soluble barium salt



is formed as a dark reddish brown precipitate, which is highly explosive.

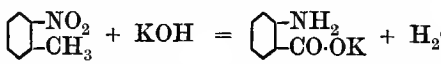
Trinitrobenzene can also form an addition-compound with potassium cyanide, which is precipitated on mixing the concentrated solutions of its components. It is a violet crystalline mass, which is very explosive. It must have the formula



With mineral acids it gives the insoluble free acid. It is remarkable that this will not react either with phosphorus pentachloride or with acetyl chloride.

The formation of similar addition-products is perhaps indicated by the peculiar behaviour of certain nitro-bodies in formic acid solution.[1] If the molecular weight is determined cryoscopically in this solvent, it is found that whereas the nitroparaffins, and those nitro-aryls (like trinitromesitylene) which have no unreplaced hydrogen attached to the nucleus, give normal values, other nitro-aryls give abnormally low values, indicating dissociation: and the more so the larger the number of negative groups (NO_2, Cl, Br, &c.) they contain. Somewhat similar results are obtained in methyl cyanide solution. Now it is scarcely possible that the nitro-aryls can dissociate (for example in the aci-form) when the nitroparaffins do not; but it is conceivable that they may form dissociating compounds with the solvent.

A remarkable reaction occurring in this group is that of *o*-nitrotoluene when heated with potash solution; the methyl is oxidized by the NO_2, with the formation of anthranilic acid (*o*-amino-benzoic acid):—

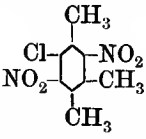


The haloid derivatives of the nitro-compounds afford a good example of the influence of nitro-groups on other substituents in the nucleus. They may be made either by nitrating the haloid compounds, which gives the ortho and para, or by chlorinating or brominating the nitro-compounds, which gives the meta derivatives, in accordance with Crum Brown's rule. If the halogen is in the ortho or para position, it is so loosely attached that it may be exchanged for hydroxyl by boiling with alkali, or for NH_2 or $NH\phi$ by heating with ammonia or aniline. The meta haloid derivatives do not show

[1] Bruni, Berti, *Atti R.* [5] **9.** i. 273, 393; Bruni, Sala, *Gaz.* **34.** ii. 479 (*C.* **00.** i. 1258; ii. 532; **05.** i. 673); Ciusa, *C.* **09.** ii. 1051.

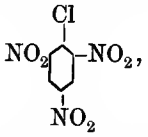
this mobility. This difference between the meta derivatives and the others is of course common to many other classes of compounds as well. No satisfactory explanation of it has been offered; but Lapworth[1] has suggested that the reactivity may be due to the intermediate formation of a compound with a quinoid ring; and its failure in the meta series to the well-known difficulty of formation of meta quinoid compounds.

If the haloid derivative contains two or more nitro-groups the halogen will react with sodium malonic or sodium acetoacetic ester. There is, however, one remarkable exception to this reactivity in dinitro-chloro-pseudocumene,



which will not react even with ammonia or aniline.

The extreme case of the influence of nitro-groups in increasing the mobility of the halogens is shown in picryl chloride (*s*-trinitro-chloro-benzene),



which exchanges its chlorine for hydroxyl on treatment with water, behaving, in fact, as an acid chloride.

NITROPHENOLS

Phenol can be nitrated, as it can be brominated, with extraordinary ease. To introduce one nitro-group it is enough to act on it with dilute nitric acid in the cold. If several nitro-groups are to be put in, a stronger acid must be used; and it is then found better to dissolve the phenol in concentrated sulphuric acid, which converts it into phenol sulphonic acid, and to treat this solution with nitric acid. In this way the violence of the reaction is modified, and the nitration facilitated; the sulphonic acid group is split off again in the process.

The products of the direct nitration of phenol are (1) ortho and para-nitrophenol, (2) *o-o-* and *o-p*-dinitrophenol, (3) picric acid (*s*-trinitrophenol). The substituents take up the same positions as in aniline.

The nitrophenols may also be obtained by various indirect methods, for example by diazotizing the nitranilines and boiling with water. The nitrophenols may be prepared on the large scale by treating the hydrocarbons with nitric acid in the presence of mercury. Under these circumstances the acid oxidizes the hydrogen to hydroxyl, being partially reduced to nitrous acid.[2]

They are colourless or yellow crystalline substances, whose salts are deep yellow or red. They are much more acidic than the phenols, and they decompose alkaline carbonates.

The nitrophenols have recently been the subject of a very important

[1] *Proc. C. S.* **14.** 159 (1898).

[2] Wolffenstein, Böters, *C.* **08. i.** 1005.

series of investigations by Hantzsch and his pupils. Their change of colour on forming salts suggests that they are probably pseudo-acids; but until lately there was very little evidence to confirm this, practically the only tests for pseudo-acids which they give being their conductivity in aqueous alcohol[1] and in pyridine.[2] The most satisfactory way of proving a difference of constitution between the nearly colourless hydrogen compounds and their strongly coloured salts would be to prepare isomeric esters, about whose constitution there could be no doubt, which should show the same difference of colour. This had never been done for any group of tautomeric substances, until it was finally effected in the case of the nitrophenols by Hantzsch and Gorke.[3] The ordinary nitrophenol ethers have long been known; they are true phenol ethers (as nitroanisol $NO_2 \cdot C_6H_4 \cdot OCH_3$) and are colourless. But besides these it was found that under special conditions isomeric ethers of a deep red colour could be obtained. They are formed by the action of alkyl iodides on the silver salts of the nitrophenols; but there are great difficulties in preparing them. All the materials must be purified with the utmost care and completely dried. The action is carried on first at 0° and then at the ordinary temperature. These precautions are necessary on account of the instability of the red ethers. They change with the greatest ease into the isomeric colourless ethers, and in the presence of traces of moisture they saponify to the free nitrophenols with extraordinary rapidity. If the proper care is taken, a mixture of the two isomeric ethers is obtained, which is separated by fractional crystallization from ether or chloroform and ligroin, the red ethers being the more soluble. These ethers are dark red in colour, the isomeric ethers being quite colourless when pure. The red ethers, whose melting-points are at least 20° lower than those of the leuco-compounds, are much more soluble in all solvents, giving a coloured solution even in water. They change over into the leuco-ethers even on standing in the solid state, the chromo-trinitrophenol ether being completely changed in a few weeks. In indifferent solvents the change is quicker, and in presence of hydrochloric acid gas almost instantaneous. Hence it has not been found possible to obtain the red ethers free from their leuco-isomers; the one which was obtained in the highest degree of purity was the trinitrophenol derivative, of which a 1·5 per cent. yield was got, still containing 10 per cent. of the leuco-ether. The red ethers were shown by the raising of the boiling-point in chloroform solution to be monomolecular.

Their saponification is extraordinarily rapid considering the relative stability of the leuco-ethers, and is quicker the more acidic the nitrophenol. Thus the trinitrophenol (picric acid) derivative is the most rapidly attacked, being rapidly saponified by water alone; the ortho-nitrophenol compound the slowest, but even this is instantaneously decomposed by sodium carbonate solution, which has no action on the leuco-ether. In this way the percentage of leuco-ether in the compound was determined.

The existence of these easily saponified isomeric ethers explains why it is often found that if the silver salt of a nitrophenol is alkylated without special

[1] *Ber.* **35.** 1001 (1902); cf. Sill, *Z. Ph. Ch.* **51.** 589 (1905).

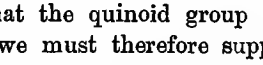
[2] Hantzsch, Caldwell, *Z. Ph. Ch.* **61.** 227 (1908).

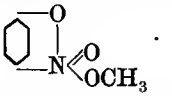
[3] *Ber.* **39.** 1073 (1906).

precautions the free nitrophenol is produced (compare the case of nitroform). It is even possible that the chromo-ether is in all cases the sole primary product, and that this then partly isomerizes to the leuco-ethers, and partly saponifies to the nitrophenol.

The chromo-ether of o-nitrophenol is a dark red oil, which was purified from the isomeric nitroanisol ($CH_3O{\cdot}C_6H_4{\cdot}NO_2$) by freezing out, though even then it contained 20 per cent. of the latter. It does not change into the leuco-compound on standing if it is quite dry. The *s*-trinitrophenol ether (which may be called the true picric ester) loses its colour in ethereal solution in three to four weeks, or, if hydrochloric acid gas is passed into the solution, in three minutes. In the case of para-nitrophenol, the chromo-ether was shown to exist, as the product was coloured and only lost its colour gradually on addition of acid, which would destroy the colour of the salt at once. But it could not be isolated.

The existence of a chromo-ether of meta-nitrophenol could only be inferred from the fact that in the alkylation free *m*-nitrophenol was produced.

Now there is no doubt that the leuco-ethers have the alkyl attached to the phenol oxygen, as in $CH_3O{\cdot}C_6H_4{\cdot}NO_2$. The chromo-ethers, having the same molecular weight, must have an isomeric structure, and must have the alkyl attached to the nitro-group. Hantzsch originally suggested for them the obvious quinoid formula  . But later work has shown that it is probable that the quinoid group alone is not sufficient to account for the colour, and we must therefore suppose in this case (as in those of the nitro-ketones and the dinitro-paraffins) that the second substituent (here the phenol hydroxyl) also comes into play. We are thus led to accept, provisionally at any rate, a formula analogous to the old peroxide formula for quinone (though without necessarily accepting that formula for quinone itself):—



The discovery of these chromo-nitrophenol ethers is of great importance in its bearing on the question of the relation between constitution and colour.[1] Without discussing this question in detail, there are two points in it to be noticed. In the first place, it was held formerly, especially by Ostwald and his school, that ionization is sufficient of itself to account for a change of colour; and that the ions have or may have a colour different from that of the undissociated molecule which produces them. But for several years past there has been an accumulation of instances in which it has been proved that the differently coloured ions had also a different constitution. Thus the great majority of indicators have been shown either actually to be pseudo-acids or pseudo-bases, or at any rate to possess structures which are characteristic of these classes of bodies. Hantzsch, to whom a great part of the evidence is due, has been led to the conclusion that all changes of colour are caused by changes of constitution, and that ionization is altogether without influence on colour. There is some reason to think that the truth lies between these

[1] Hantzsch, *Ber.* **39.** 1084 (1906).

two extremes, though much more on the side of Hantzsch; and that ionization may affect the depth of colour to some extent, but not its tint, so that from the qualitative point of view (with which we are mainly concerned) Hantzsch's doctrine may be accepted. Whenever we get a distinct change of tint, and especially whenever we get the change of a colourless into a coloured body or vice versa, we are justified in assuming that a change of constitution has occurred.

The second question concerns the structures which are required to produce colour. Witt's theory of chromophor and auxochrome (in its original form,[1] and not as subsequently modified to apply to dyes) is an excellent empirical guide to this problem. According to this theory there are certain groups, for example the azo-group, the quinone ring, and the nitro-group, which tend to be coloured, and are known as chromophors; and certain other groups, the auxochromes, such as hydroxyl, methoxyl, NH_2, &c., which are not in themselves coloured, but which, when they occur in the same molecule as a chromophor, increase its colour to a greater or less extent.

A controversy has been going on lately between Hantzsch and Kauffmann as to the relation between colour and constitution, which appears at first sight to be a dispute as to the validity of Witt's theory, but is really concerned only with the interpretation of the facts. To take a concrete instance: nitrobenzene when pure is colourless; if a hydroxyl is introduced (giving nitrophenol) it becomes feebly coloured; if the hydrogen is replaced by metal it becomes strongly coloured. Witt would say that the nitro-group is a chromophor, the hydroxyl a weak and the MO group a strong auxochrome. This is merely a clear restatement of the facts. The question at issue is why this is so. The older theory scarcely concerned itself with this: it considered that the mere 'passive coexistence' of chromophor and auxochrome was sufficient to account for the colour. The modern defenders of the theory, such as Kauffmann, conscious of a certain weakness at this point, speak of a mysterious influence, not to be too closely examined, exerted by the auxochrome on the delicate structure of the molecule. As against this view, Hantzsch adopts a clear and definite standpoint. He holds in fact, though not perhaps explicitly, that the colour is au additive property, in this sense, that every group exerts its own influence on the absorption of light independently of the other groups present. Thus the fact that nitrobenzene is colourless shows that the group $\phi\cdot NO_2$ has no effect on visible light. The same must be true of the group KO attached to the nucleus, since $KO\cdot\phi$ has no colour. Hence the body $KO\cdot C_6H_4\cdot NO_2$ must be colourless also, and as potassium nitrophenol is coloured it cannot be represented by this formula. Since a new effect—the production of colour—results from the simultaneous presence of KO and NO_2 in benzene which does not occur with either of them separately, a new structure must have been produced by the interaction of these two groups (the chromophor and the auxochrome) with one another and with the benzene nucleus, as may be represented, for example, by the quinoid formula $O{=}C_6H_4{=}NO\cdot OK$, or in other ways. The difference and the superiority of

[1] *Ber.* **9.** 522 (1876).

Hantzsch's view lie in the fact that he looks for definite changes of structure as accompanying colour changes. The advantages of this are obvious. There is abundant evidence that change of colour is an indication of change of structure, and that it is one of the most valuable—just because it is one of the most obvious—proofs that we possess of tautomeric change. We may therefore disregard Kauffmann's view, and consider what light Hantzsch's theory throws on the question of the structure of the nitrophenols and their derivatives.

All[1] true (i. e. not aci-) nitrohydrocarbons, whether fatty or aromatic, whether they contain one or several nitro-groups (as trinitrobenzene, nitroform, tetranitromethane, &c.), have been shown to be colourless when pure, though in some cases the purification is a matter of some difficulty. So are also all substituted nitrobenzenes with unalterable substituents, i. e. substituents which cannot go over into tautomeric forms, as OAlk, OAc, with one exception to be discussed later. The only nitro-aromatic compounds which are coloured are: many nitrophenols, some of their ethers, and all of their salts. The existence of the two series of ethers makes it certain that the nitrophenols are tautomeric, giving derivatives of two forms, one $C_6H_4\langle^{OH}_{NO_2}$, colourless, and the other, provisionally assigned the quinoid formula, $C_6H_4\langle^{O}_{NO\cdot OH}$, coloured.

Many free nitrophenols are either absolutely or almost absolutely colourless (*p*-nitrophenol, 2,4-dinitrophenol, 2,4,6-trinitrophenol); they are therefore practically entirely the true nitro-form. Others, like *o*-nitrophenol, are quite distinctly coloured, but much less so than their salts. This suggests that they are partly in the chromo-form, but mainly in the other. To this there is an apparent objection, for Knorr has shown that, except at its hypothetical transition point, a solid tautomeric substance can only be in one form. But this proof depends on the assumption that the two solid forms constitute two distinct phases; and it is possible for a solid solution of the two solid forms to exist as a stable substance. Hantzsch assumes (with great probability) that this happens with the two forms of the nitrophenols, as he had previously done for the solid diazonium halides. The proportion of the two forms will depend on the substance and also on the temperature: and it is found that as a fact all nitrophenols in the solid state (as also in solution) get darker on heating.

The salts of the nitrophenols with the alkalies and alkaline earths, which are always much darker than the free hydrogen compounds, must be practically entirely in the much more acidic chromo-form. These salts, like those of the α-nitro-ketones and the dinitroparaffins, occur in two series,[2] one yellow and one red, this difference not depending on the state of hydration. Hence the nitrophenols can give two series of chromo-derivatives, the salts belonging to both series, the ethers, as far as they are yet known, only to one.

In solution the free nitrophenols are coloured, and hence the two forms are present in equilibrium, the proportions depending largely on the solvent. In this respect the order of solvents is the same as that observed by Wislicenus and Claisen for the keto-enolic equilibrium: ligroin nearly colourless: (nearly

[1] Hantzsch, *Ber.* **39.** 1084 (1906).

[2] Hantzsch, *Ber.* **40.** 330 (1907).

all true nitro)—chloroform pale—benzene rather darker—alcohol and ether distinctly darker—water darker still. In other words, the chromo-form is favoured by an increase of the dielectric constant, as it is by a rise of temperature.

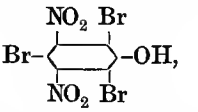
In an aqueous solution of a nitrophenol we have the following substances present:—

(1) $Ar\langle^{OH}_{NO_2}$; (2) $Ar\langle^{O}_{NO\cdot OH}$; (3) $Ar\langle^{O}_{NO\cdot O'}$; (4) $H^{\cdot}$,

omitting the ions of the practically undissociated true nitrophenol (1). Of these the coloured substances are (2) and (3), while the conducting substances are (3) and (4). Experiments on an aqueous solution of 2,4-dinitrophenol showed that the dissociation (up to 30 per cent.) and the colour remained proportional, showing that the amount of undissociated coloured aci-form present was negligible. If a strong acid, such as hydrochloric acid, is added to a solution of a nitrophenol in water, the consequent increase of hydrogen ions will drive back the dissociation of the aci-form, and so in order to restore equilibrium a corresponding quantity of this must go over into the colourless form and the colour must diminish. Experiment showed that this was the case. The colour of picric acid solution (at a dilution of 1,145 litres) diminishes to 68 per cent. of its original value on adding half normal hydrochloric acid, and to 20 per cent. if the acid is made ten times normal. Ortho-nitrophenol also becomes paler on addition of acid, but it is still distinctly yellow even in concentrated hydrochloric acid, where it must be practically undissociated: so that even in this case a perceptible quantity of the aci-form must be present.

The salts of the nitrophenols are sometimes yellow and sometimes red; in certain cases salts of an intermediate orange colour are obtained, but these can be separated by careful recrystallization into a yellow and a red component. These latter are probably in most cases only mixtures of the two salts; but sometimes their colour deepens on warming, and returns to its original shade on cooling. In such instances it is probably a solid solution of one form in the other.[1] It is often found, where both salts can be obtained from the same alkali and the same nitrophenol, that they differ in the amount of water which they contain; but the fact that it is sometimes one form and sometimes the other which is hydrated shows that the water is not necessary to either form, but merely determines (in the same way that the alkali metal does) which is the stable modification in that particular case.

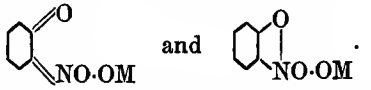
One of these bodies, *s*-tribromo-meta-dinitro-phenol,



gives two isomeric potassium salts, one yellow and one red, of the same composition; they give different solutions of their own respective colours, but of the same molecular weight and conductivity.

[1] Korczynski, *Ber.* **42**. 167 (1909), finds that the red salts of the same nitrophenol with different alkalies differ in depth of colour; and hence infers that they are themselves solid solutions of a darker form in a lighter.

These two series of salts must have two different constitutional formulae. The structure $MO{\cdot}C_6H_4{\cdot}NO_2$ is obviously excluded as colourless, since the corresponding ether is colourless. It is conceivable that one series might correspond to the peroxide and the other to the diketone structure of quinone :—



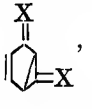
To this there is the objection that such isomerism would be possible in other quinone derivatives as well, while it would not be possible in fatty compounds. Now this occurrence of two isomeric series of differently coloured salts has not been observed with any quinone derivatives not containing nitrogen, while on the other hand it is exactly repeated in the nitro-ketones and in the dinitroparaffins. This would seem to show that it is of a kind which does not depend on the peculiarities of the quinone ring. This points to stereoisomerism as the cause, and we already have a parallel case in the syn and anti diazo-sulphonates, of which the former are dark in colour while the latter are light.

As it is reasonable to assume a direct connexion between the nitro-group and the phenol oxygen, we may take the peroxide formula of quinone as the basis, and write the isomers



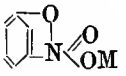
Now the red ethers, which must correspond to the red salts, go over very easily into the colourless phenol ethers ; this suggests that they have the OK group close to the phenol oxygen, and so have the α formula, in which case the yellow salts would have the β structure.

These phenomena of isomerism among the nitrophenol salts occur in all three series, ortho, meta, and para: indeed it is in the meta series that the isomers have been separated. And unless we are to assume that the meta salts have a structure entirely different from that of the ortho and para, we must admit the possibility, which is generally denied, of meta quinones. But the formulation which Hantzsch adopts gives us a way out of this difficulty. There is no doubt that the quinones themselves and many of their simpler derivatives, such as the imides and oximes, which are well known in the ortho and para series, have never been prepared, and so far as we can see cannot exist, in the meta series. But for such compounds, and especially for the quinones themselves and their oximes, the diketone formula is far more probable than the peroxide ; and it is quite conceivable that this is why the meta derivatives do not exist in these cases, the grouping



which we should have to assume in them, being impossible. But if Hantzsch

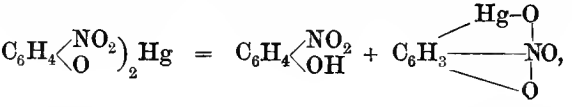
is right in thinking that in the nitrophenol salts we have derivatives of the peroxide formula, it does not in the least follow that the structure



of the meta derivatives of this type is impossible. If so, it is perhaps a mistake to speak of such a formula as 'quinoid', but the name has been accepted, and it is a convenience to retain it, as long as the questions of structure are still undecided.

This isomerism of the salts is not confined to those of the alkali metals. It is observed in the thallium salts of picric acid[1]; and in the mercuric salts very peculiar relations are found.[2] Mercury is of course much less positive than the alkali metals, and its salts are remarkable for their low degree of ionization, frequently not greater than that of the acid from which they are derived. Accordingly we find that the properties, and especially the colour, of the true mercuric salts of the nitrophenols, such as $\left(C_6H_4\langle^{NO_2}_{O}\right)_2Hg$, resemble those of the free nitrophenols themselves. They must therefore be mixtures or solid solutions of the normal and aci-form $C_6H_4\langle^{NO_2}_{O\cdot hg}$ and $C_6H_4\langle^{NO\cdot Ohg}_{O}$.

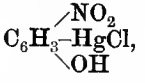
But, as Dimroth has shown, the mercury atom in the salts of aromatic compounds has a strong tendency to migrate to the ring; and in these compounds this actually occurs. If they are boiled with water they split off one molecule of free nitrophenol, and form deeply coloured anhydrides:—



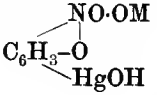
in which the mercury is attached on one side to the nitro-group, and on the other directly to the benzene ring. They are exactly analogous, for example, to Dimroth's mercuri-benzoic anhydride

$$C_6H_4\langle^{Hg}_{CO}\rangle O.$$

They are non-electrolytes and give no reactions of the mercuric ion. If they are treated with strong acid the ring breaks between the mercury and the nitro-group, the mercury remaining attached to the nucleus, and a salt, such as



is formed, which is colourless or only faintly coloured. The same breaking of the ring is produced by alkalies, giving, for example,

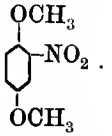


[1] Rabe, *Z. Ph. Ch.* **38**. 175 (1901).

[2] Hantzsch, Auld, *Ber.* **39**. 1105 (1902).

but these, of course, are coloured, being the aci-salts of substituted nitrophenols. The position of the mercury on the ring is by preference ortho or para to the nitro-group, but it can be meta.

It has been mentioned that there is one exception to the rule that nitro-compounds with unchangeable substituents are colourless. This is nitrohydroquinone methyl ether,[1]



A body with this formula we should expect to be always colourless; and as a matter of fact in most non-dissociating solvents it is so, but not in others. Hantzsch has made a careful study of its properties in various solvents. In dissociating solvents it gives strongly coloured (yellow) solutions, the colour being roughly proportional to the dielectric constant. The molecular weight is practically normal both in the nearly colourless hexane solution and in the deep yellow solution in methyl alcohol. The colour shows a slight tendency to increase with the concentration, but this may be only experimental error. The yellow solutions are non-conductors, so that a dissociated form is not produced. The colour seems to be unaffected by temperature.

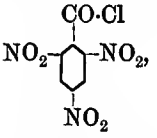
It is evident that the colourless form is the true hydroquinone ether, whose formula is given above. In solution this changes into a yellow isomer, the equilibrium between the two depending on the solvent, and the yellow form being favoured by solvents of high dielectric capacity. But what this yellow form may be it is at present impossible to say.

Picric acid, symmetrical trinitrophenol, has long been known. It is formed by the action of nitric acid on many organic substances, such as indigo, aniline, resin, silk, and leather. It is generally prepared by the action of nitric acid on a solution of phenol in concentrated sulphuric acid. It is the oldest artificial dye. The free substance is pale yellow, but its aqueous solution and that of its salts are much more deeply coloured. It is found[2] that its alcoholic solution becomes much paler when it is cooled with liquid air, and that the solid under these conditions is almost white. This indicates a displacement of the equilibrium between the two forms, and seems to show that the free substance is a solid solution. It is remarkable that its solution in anhydrous ether[3] is almost colourless, but turns yellow on adding a drop of water, a fact which can be used to detect the presence of water in ether. This addition of a trace of water also greatly increases the solubility in ether.[4] Picric acid can be used to dye animal fibres directly, but the colour is not very fast. It is now practically abandoned as a dye, but is manufactured in hundreds of tons for use as an explosive,[5] especially in war, on account of the ease with which it is prepared, and the fact that it is not liable to be exploded by an accidental blow. Its salts explode when struck, but the free acid requires a detonator. The so-called melinite bombs are filled with molten

[1] Hantzsch, *Ber.* **40.** 1556 (1907). Cf. Hantzsch, Staiger, *Ber.* **41.** 1204 (1908).
[2] Heiduschka, *C.* **07.** i. 572. [3] Bougault, *C.* **03.** ii. 565. [4] Cobet, *C.* **06.** i. 233.
[5] Will, *Ber.* **37.** 294 (1904).

picric acid, and fitted with gun-cotton detonators. In the laboratory picric acid is often used to identify bases, with which it forms well crystallized and sparingly soluble salts, and also many hydrocarbons, with which it forms crystalline addition compounds. A strong solution of sodium picrate may be used as a qualitative test for potassium, giving a precipitate with a potassium salt, owing to the fact that sodium picrate is twenty-six times as soluble in cold water as the potassium salt.

Symmetrical trinitrobenzoic acid, which has already been referred to in connexion with the nitronic acids, affords a striking instance of the inactivity (due to stereo-hindrance) of the derivatives of the di-ortho-substituted benzoic acids. Its chloride,



is by far the most stable acid chloride known. It is largely undecomposed even after boiling with water for an hour. This is the more remarkable since in picryl chloride, which differs from trinitrobenzoyl chloride only in not having the CO between the chlorine and the nucleus, the effect of the nitro-groups is to loosen the attachment of the chlorine so much that it is removed by water. The stability of the acid chloride is of course due to its protection by the nitro-groups, which prevent the water molecules from coming up to react with it. But it is difficult to see why in picryl chloride the nitro-groups should not exert a similar protective influence.

NITRO-DIPHENYLAMINES

The nitro-derivatives of diphenylamine closely resemble the nitrophenols in their colour relations. They can be shown to be pseudo-acids by their conductivity in pyridine, and while they themselves have only a pale colour, their salts are deeply coloured. It has recently been shown by Hantzsch and Opolski[1] that this analogy extends to their alkyl derivatives as well. Thus hexanitro-diphenylamine, $(NO_2)_3C_6H_2{\cdot}NH{\cdot}C_6H_2(NO_2)_3$, and its methyl derivative, $(NO_2)_3C_6H_2{\cdot}N(CH_3){\cdot}C_6H_2(NO_2)_3$, are only feebly coloured, while the salts form two series, one red and the other violet. By a method exactly similar to that used for making the chromo-ethers of the nitrophenols (treatment of the silver salt with alkyl iodide at a low temperature in complete absence of moisture) it yields an isomeric methyl ether, forming black crystals which give a violet solution in benzene. This is only produced in small quantity and is very unstable, going over into the normal isomer when heated above its melting-point, and even at the ordinary temperature in many solvents, and being almost instantaneously saponified by acids. As with the nitrophenols, the chromo-ether has the lower melting-point (chromo-ether 140°, leuco-ether 236–7°), but in this case it is less soluble in all solvents than its leuco-isomer. It is to be noticed that in both cases the colour of the chromo-ether is that of the more deeply coloured series of salts.

[1] *Ber.* **41**. 1745 (1908).

CHAPTER VIII

CARBONIC ACID DERIVATIVES

Carbonic acid, $C{=}O(OH)_2$, being a dibasic acid, can give:—

1. A monamide $C{=}O(NH_2)(OH)$ carbamic acid, which cannot exist in the free state, but is known in the form of salts and esters, the latter being the so-called urethanes.

2. A diamide $C{=}O(NH_2)_2$ carbamide or urea.

3. An amidine $C{=}NH(NH_2)(OH)$ tautomeric with urea. There is evidence for the existence of this form among the derivatives of urea.

4. A di-imide $C(NH)_2$, of which only a few derivatives are known.

5. An amidine-amide $C{=}NH(NH_2)_2$, the amidine of carbamic acid, which is guanidine.

It can also form (6) an imide, $\overset{\frown}{CO}\,NH$, which is isocyanic acid, but this is more conveniently dealt with among the cyanogen compounds.

Those derivatives which contain oxygen can have this oxygen replaced by sulphur; and the thio-compounds so produced are of considerable importance.

Carbamic acid, the monamide of carbonic acid, occurs only in the form of salts and esters.

The ammonium salt is produced by the direct union of carbon dioxide and ammonia:—

$$C(O)_2 + 2\,NH_3 = C{=}O(NH_2)(O{\cdot}NH_4).$$

It is best obtained by passing carbon dioxide and ammonia simultaneously into cooled absolute alcohol, when it is deposited as a crystalline powder. It occurs in commercial ammonium carbonate, which is made by subliming a mixture of ammonium sulphate and calcium carbonate; that is, by the condensation of a mixture of equal volumes of water vapour, carbon dioxide, and ammonia. If they were completely condensed they would form ammonium carbonate, but some of the water escapes.

A solution of ammonium carbamate when treated with dilute calcium chloride

solution gives no precipitate at first; but on standing, or more rapidly on heating, calcium carbonate is thrown down, owing to the carbamate taking up water. Under these conditions the hydrolysis is complete, as the carbonate is removed from the solution as quickly as it is formed. But if the carbamate is treated with water alone in the absence of the calcium salt, the reaction is found[1] to be reversible, an equilibrium between carbamate and carbonate being established. On treatment with mineral acids it is saponified at once, giving an ammonium salt and carbon dioxide. On the other hand, as the ammonium salt of a carboxylic acid, it breaks up when heated in a sealed tube into its amide—urea—and water:—

$$\begin{matrix} NH_2 \\ C{=}O \\ O{\cdot}NH_4 \end{matrix} = \begin{matrix} NH_2 \\ C{=}O \\ NH_2 \end{matrix} + H_2O.$$

The acid chloride of carbamic acid, carbamic chloride, is obtained by passing hydrochloric acid gas over heated metallic cyanates:—

$$O{=}C{=}NH + HCl = O{=}C\begin{matrix} NH_2 \\ Cl \end{matrix},$$

or by passing carbonyl chloride over heated ammonium chloride:—

$$\begin{matrix} Cl \\ C{=}O \\ Cl \end{matrix} + NH_3 = \begin{matrix} NH_2 \\ C{=}O \\ Cl \end{matrix} + HCl.$$

It is a colourless liquid which boils at 61–62°, breaking up partially into cyanic and hydrochloric acids, which recombine to form carbamic chloride in the receiver; but mainly into hydrochloric acid and a polymer of cyanic acid, cyamelide. This latter decomposition occurs fairly soon if the chloride is allowed to stand at the ordinary temperature. As an acid chloride it is violently decomposed by water to give ammonium chloride and carbon dioxide; with ammonia or amines it forms ureas, and with alcohols, the esters of carbamic acid or urethanes:—

$$\begin{matrix} NH_2 \\ C{=}O \\ Cl \end{matrix} + C_2H_5OH = \begin{matrix} NH_2 \\ C{=}O \\ OC_2H_5 \end{matrix} + HCl.$$

If the alcohol is treated with excess of carbamic chloride, this excess reacts with the urethane as with an amine to give an allophanic ester:—

$$H_2N{\cdot}CO{\cdot}Cl + H_2N{\cdot}CO{\cdot}OC_2H_5 = H_2N{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}OC_2H_5 + HCl.$$

With benzene and aluminium chloride carbamic chloride reacts according to the Friedel and Crafts method to form benzamide:—

$$H_2N{\cdot}CO{\cdot}Cl + C_6H_6 = H_2N{\cdot}CO{\cdot}C_6H_5 + HCl.$$

The alkyl-substituted carbamic chlorides are got by passing carbonyl chloride over heated amine hydrochlorides. When they are distilled over lime they behave as carbamic chloride itself does when heated alone, and break up into hydrochloric acid which combines with the lime, and isocyanic esters:—

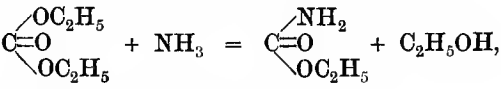
$$CH_3{\cdot}NH{\cdot}CO{\cdot}Cl = HCl + CH_3{\cdot}N{=}C{=}O.$$

The phenyl derivatives are obtained in the same way.

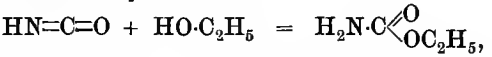
[1] Macleod, Haskins, *C.* **06.** i. 1820.

The esters of carbamic acid or *urethanes* are obtained:—

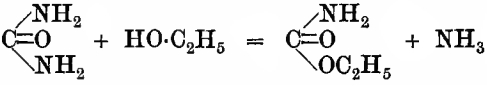
1. From carbonic or chlorocarbonic ester and ammonia:—



2. From the alcohol and cyanic acid:—



3. By the action of alcohol on urea at a high temperature:—



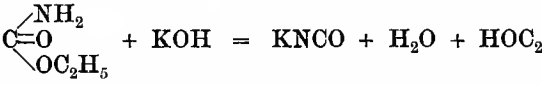
This is a reversal of the ordinary formation of amides by the action of ammonia on the esters.

4. They may be prepared, as has been shown, by treating carbamic chloride with alcohol.

By substituting in these reactions amines for ammonia, or isocyanic esters for cyanic acid, alkyl substituted urethanes can be obtained.

The simple urethanes are crystalline, the alkyl urethanes liquid. They all boil without decomposition.

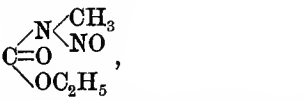
The simple urethanes give with potash potassium cyanate:—



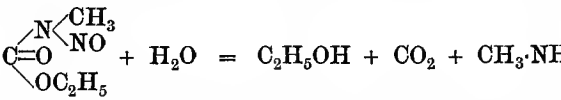
When their solution in benzene is treated with sodium they give a quantitative yield of sodium cyanate[1]:—



The mono-alkyl urethanes, when treated with nitrous acid, give nitroso-derivatives, such as nitroso-methyl-urethane,



according to the general reaction for secondary amines and amides. These nitroso-urethanes show a remarkable behaviour on saponification, which can best be explained by supposing that they first yield the very unstable nitroso-primary amine:—

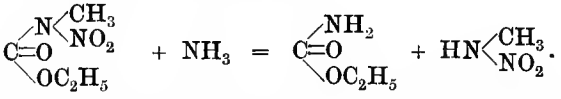


This methyl nitrosamine then breaks up according to the conditions of the experiment to give either an open-chain diazo-compound $CH_3{\cdot}N{:}NOK$, or diazomethane CH_2N_2, or methyl alcohol and nitrogen.

The mono-alkyl urethanes on treatment with anhydrous nitric acid are nitrated in the NH group, and the products when treated with ammonia split

[1] Leuchs, Geserick, *Ber.* **41**. 4171 (1908).

up, regenerating urethanes, and forming nitramines, which, being comparatively stable bodies, are not further decomposed :—



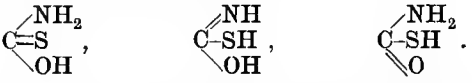
The simple urethanes give sodium derivatives in which the amide hydrogen is replaced, such as NHNa·CO·OEt. These bodies[1] react with esters as amines, giving amides, for example, with phenyl acetic ester :—

$$\phi\cdot CH_2\cdot CO\cdot OEt + NHNa\cdot CO\cdot OEt = \phi\cdot CH_2\cdot CO\cdot NH\cdot CO\cdot OEt + NaOEt.$$

The tendency to this reaction is so strong that it even takes place with haloid esters, such as chloracetic ester, which forms $CH_2Cl\cdot CO\cdot NH\cdot CO\cdot OEt$, instead of sodium chloride being eliminated, as we should expect.

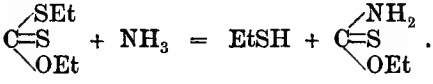
Ordinary urethane, when treated with bromine[2] in alkaline solution, gives an amido-bromide $C_2H_5O\cdot CO\cdot NBr_2$, an unstable oil. In neutral solution bromine has scarcely any action except in the presence of a carrier, such as iron wire ; but in that case the bromine attacks the ethyl group, splitting off bromal $CBr_3\cdot CHO$.

The sulphur derivatives of carbamic acid can occur in various forms : thus three mono-thio-derivatives are possible :—



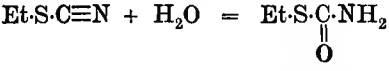
The free acids are tautomeric, differing only in the position of the hydrogen atoms and the double bond. They belong to the same highly tautomeric class of bodies as the thio-acids and the thio-amides. Free thiocarbamic acid is unstable, but its salts are known. The ammonium salt is formed by the combination of carbon oxysulphide and ammonia. If, however, the hydrogen atoms are replaced by alkyl groups, these groups are incapable of tautomerizing. It is obvious that the monoalkyl derivatives can be of three kinds, according as the alkyl is attached to nitrogen, sulphur, or oxygen. Of these three classes two are known, the sulphur and oxygen esters. The nitrogen derivatives would still be acids, and hence would share the instability of thiocarbamic acid itself.

The O-esters are obtained from the dithio-carbonic esters by the action of ammonia (normal formation of amides) :—



Their constitution is shown by their breaking up when treated with aqueous alkali to give alcohol and a thiocyanate.

The S-esters are got by the partial hydrolysis of thiocyanic esters with alcoholic hydrochloric acid :—



[1] Diels, Heintzel, *Ber.* **38.** 297 (1905).

[2] Diels, Ochs, *Ber.* **40.** 4571 (1907).

Their constitution is proved by their method of formation, and by the fact that on saponification they yield mercaptans.

Dithio-carbamic acid $C\begin{cases}NH_2\\S\\SH\end{cases}$ or $C\begin{cases}NH\\SH\\SH\end{cases}$ is obtained in the form of its ammonium salt by the combination of ammonia and carbon disulphide; and this salt on treatment with dilute sulphuric acid gives the free acid as an unstable reddish oil.

A dialkyl derivative of this ammonium salt is formed by the action of carbon disulphide on fatty amines:—

$$C\begin{cases}S\\S\end{cases} + 2\,NH_2Et = C\begin{cases}NHEt\\S\\S{\cdot}NH_3Et\end{cases}.$$

This reaction is generally said to distinguish the fatty amines from the aromatic, which under these conditions give a diaryl thiourea (e. g. aniline gives thiocarbanilide); but it has recently been shown that some aromatic amines will form dithiocarbamates in presence of ammonia.[1]

Carbamic acid is the mono-carboxylic acid of ammonia, $NH_2{\cdot}COOH$. The corresponding dicarboxylic acid, $NH(COOH)_2$, the so-called *imino-dicarboxylic acid*, is also known in the form of certain derivatives.[2] Its neutral esters are obtained by the action of chloro-carbonic ester on the sodium urethanes:—

$$HN\begin{cases}Na\\CO{\cdot}OEt\end{cases} + Cl{\cdot}CO{\cdot}OEt = HN\begin{cases}CO{\cdot}OEt\\CO{\cdot}OEt\end{cases} + NaCl.$$

This is a crystalline body, M.Pt. 50°, B.Pt. 215°. It is to be observed that this ester is more acidic than urethane. If it is treated with sodium urethane, the sodium passes over to the nitrogen of the dicarboxylic ester.[3]

If this sodium imino-dicarboxylic ester is again treated with chloro-carbonic ester, the last hydrogen on the nitrogen is replaced by carboxethyl, and nitrogen tricarboxylic ester[4] is produced.

$$N\begin{cases}CO{\cdot}OEt\\Na\\CO{\cdot}OEt\end{cases} + Cl{\cdot}CO{\cdot}OEt = N\begin{cases}CO{\cdot}OEt\\CO{\cdot}OEt\\CO{\cdot}OEt\end{cases} + NaCl.$$

This body, a liquid boiling at 146° under 12 mm. pressure, corresponds to a triamide like triacetamide $N(CO{\cdot}CH_3)_3$, and accordingly is very easily saponified to alcohol, carbon dioxide, and imino-dicarboxylic ester. If it is treated with anhydrous ferric chloride, it splits up in an unusual manner, to give carboxethyl isocyanate and ethyl carbonate[5]:—

$$N\begin{cases}CO{\cdot}OEt\\CO{\cdot}OEt\\CO{\cdot}OEt\end{cases} = O{=}C{=}N{\cdot}CO{\cdot}OEt + C\begin{cases}OEt\\=O\\OEt\end{cases}.$$

The monamide of imino-dicarboxylic acid is allophanic acid $HN\begin{cases}CO{\cdot}NH_2\\CO{\cdot}OH\end{cases}$, or $C\begin{cases}NH_2\\=O\\NH{\cdot}CO{\cdot}OH\end{cases}$ (urea carboxylic acid), and its diamide is biuret $HN\begin{cases}CO{\cdot}NH_2\\CO{\cdot}NH_2\end{cases}$, which is one of the products of the action of heat on urea.

[1] Losanitsch, *Ber.* **40.** 2970 (1907).
[2] Kraft, *Ber.* **23.** 2786 (1890).
[3] Diels, *Ber.* **36.** 736 (1903).
[4] Diels, Nawiasky, *Ber.* **37.** 3672 (1904).
[5] Diels, Wolf, *Ber.* **39.** 686 (1906).

UREA

This body is memorable in the history of chemistry from the fact that its formation from ammonium cyanate by Wöhler in 1828 went far to break down the barrier which had been set up between organic and inorganic chemistry. It is of course incorrect to describe this as a synthesis of an organic substance from inorganic materials; but it was the first case in which a body admittedly of an organic nature was produced from a material which was regarded as belonging to the class of inorganic compounds. It is not a little remarkable that John Davy had obtained urea several years before this by the action of carbonyl chloride on ammonia, but had not recognized it.

Wöhler's method, of heating ammonium cyanate, is still used for the preparation of urea. The reaction occurs on evaporating the aqueous solution; but it is reversible, and hence the conversion is never complete. It has been investigated in great detail by Walker and Hambly,[1] who find that the change of ammonium cyanate into urea is much more rapid than the reverse change, equilibrium being reached in a decinormal solution when there is about 95 per cent. of urea and 5 per cent. of cyanate present. This equilibrium is little affected by the temperature. Their method of titration was to treat a known volume of the solution with an excess of silver nitrate, whereby the cyanate was precipitated as the almost insoluble salt, while the urea did not react. It was found that the formation of urea from the cyanate was not, as might have been expected, monomolecular, but bimolecular, the velocity being proportional to the square of the concentration of the ammonium cyanate. Further examination showed that while the addition of indifferent salts such as potassium sulphate, or of ammonia, had very little influence on it, it was greatly increased by adding either a cyanate or an ammonium salt. This proves that the two molecular species, to the product of whose concentration the velocity is proportional, are $NH_4^{\cdot}$ and CNO'. The salt being highly dissociated at the dilutions employed, the concentration of each of these ions will be nearly equal to that of the salt, when no other substance is present, and therefore the variation in the velocity with the dilution will be that required for a bimolecular reaction. The addition of a salt like potassium sulphate will not affect the concentration of these ions, and will therefore not affect the velocity either. On the other hand, if we add to the solution either a cyanate or an ammonium salt, we shall increase the concentration of one or other of the two ions, and hence also the velocity of the reaction. This explains also why it is that ammonia does not increase the velocity, while an ammonium salt does so. The addition of ammonia does not appreciably affect the concentration of the NH_4 ions, because, as a very weak base, it is only ionized to a minute extent, especially in the presence of an ammonium salt.

From these experiments Walker infers that it is the ions of the ammonium cyanate which change into urea, and not the undissociated cyanate. But this conclusion, though it was accepted for many years, is not really valid. If we assume that the salt obeys Ostwald's law, we have in solution the equilibrium :—

$$K \times C_{NH_4CNO} = C_{NH_4} \times C_{CNO'}.$$

[1] *J. C. S.* **1885**. 746; Walker, Appleyard, ib. **1896**. 193; Walker, Kay, ib. **1897**. 489.

Now what Walker showed is that the rate of formation of urea is proportional to the right-hand side of this equation. It follows that it must also be proportional to the left-hand side: that is, to the concentration of the undissociated portion of the ammonium cyanate. But this is what we should find if it was only the undissociated portion, and not the ions, which formed urea. Moreover, the addition of excess of either ion, i.e. of an ammonium salt or a cyanate, will alter the concentration of the undissociated salt in the same proportion as it alters the product of the concentration of the two ions. Thus the results obtained by Walker are equally compatible either with the view that it is the ions which undergo the change, or with the view that it is only the undissociated part of the salt which does so. Subsequent investigations have shown that it is on the whole more probable that the reaction is due to the undissociated portion of the salt.

The substitution of alkyl ammonium cyanates[1] for ammonium cyanate affects the velocity constants of the reaction, generally diminishing them; but no regularities could be observed.

Another remarkable method[2] of making urea from inorganic constituents is by heating a solution of carbon monoxide in ammoniacal cuprous chloride, when metallic copper separates and urea is formed:—

$$CO + 2\,NH_3 + Cu_2Cl_2 = H_2N{\cdot}CO{\cdot}NH_2 + 2\,HCl + 2\,Cu.$$

There are two other methods of formation which are of interest as showing the constitution of urea, firstly J. Davy's synthesis from phosgene and ammonia, which is best carried out by acting with the phosgene on sodium phenate, so as to give phenyl carbonate, and then warming the phenyl carbonate in a stream of ammonia:—

$$\begin{array}{l} \mathrm{Cl} \\ \mathrm{C{=}O} \\ \mathrm{Cl} \end{array} + \begin{array}{l} \mathrm{NaO}\phi \\ \\ \mathrm{NaO}\phi \end{array} = 2\,\mathrm{NaCl} + \begin{array}{l} \mathrm{O}\phi \\ \mathrm{C{=}O} \\ \mathrm{O}\phi \end{array} :$$

$$\begin{array}{l} \mathrm{O}\phi \\ \mathrm{C{=}O} \\ \mathrm{O}\phi \end{array} + 2\,NH_3 = 2\,H\mathrm{O}\phi + \begin{array}{l} \mathrm{NH_2} \\ \mathrm{C{=}O} \\ \mathrm{NH_2} \end{array} :$$

and secondly, the partial saponification of cyanamide:—

$$\begin{array}{l} \mathrm{N} \\ \mathrm{C} \\ \mathrm{NH_2} \end{array} + H_2O = \begin{array}{l} \mathrm{NH_2} \\ \mathrm{C{=}O} \\ \mathrm{NH_2} \end{array}.$$

Urea forms long colourless prisms, melting at 132–133°; it is easily soluble in alcohol, and very easily in water. It is a fairly strong monacid base, and forms stable salts with acids, one of which, the nitrate, is often used for isolating it, as it is only slightly soluble in water, and nearly insoluble in strong nitric acid.

Urea is the most important form in which nitrogen is excreted from the animal organism, and it is also found[3] in various animal fluids, such as blood and lymph, though generally only in small quantities. It has also been found in certain plants.[4]

As an amide, urea is saponified by acids and alkalies, forming carbonic acid

[1] Walker, Appleyard, *J. C. S.* **1896**. 193. [2] Jouve, *C.* **99**. i. 422.
[3] Bamberger, Landsiedl, *C.* **03**. ii. 56.
[4] For theories as to its origin in the animal body cf. Eppinger, *C.* **05**. ii. 151.

and ammonia. The velocity of this change has been examined with somewhat unexpected results by Fawsitt.[1] He determined the extent to which the reaction had proceeded by titrating the liquid with acid and methyl orange, which measured the ammonia produced. According to the equations usually given :—

$$CO(NH_2)_2 + 2\,HCl + H_2O = 2\,NH_4Cl + CO_2,$$
$$CO(NH_2)_2 + 2\,NaOH = Na_2CO_3 + 2\,NH_3,$$

we should expect the reaction in both cases to be of the third order, where the initial concentration of acid or alkali was that required by this equation. But experiment showed that in both cases it was of the first order. Where acid was used, it was found that its concentration had little influence on the velocity, unless it was great, when the velocity was somewhat diminished. With alkalies, an increase in concentration somewhat increased the velocity.

The results obtained with acid can be explained as follows. We know from Walker and Hambly's work that urea changes in aqueous solution into ammonium cyanate, though this change stops when about 5 per cent. of the urea has gone over. Now ammonium cyanate was found to be very rapidly saponified by acid to ammonia and carbon dioxide. If, therefore, we suppose that the direct saponification of the urea does not occur at all, or only slowly, we shall have the urea changing over into cyanate, and this decomposing almost as fast as it is formed. In this case, as long as the concentration of acid is sufficient to prevent the accumulation of cyanate, and thereby to stop the back action, it will not affect the velocity, which will be that of the tautomeric change, and will be proportional to the amount of urea present. We shall thus get the values required for a monomolecular reaction, as is found to be the case. The diminution of velocity produced by a large quantity of acid is due to the conversion of part of the urea into its salt, which does not undergo the change into ammonium cyanate, and is thus withdrawn from the reaction. This view is confirmed by the fact that the initial velocity (when there is practically no cyanate present) of disappearance of urea is nearly the same in pure water as when acid is added, and that it has the same temperature coefficient.

With alkali the case is different. The decomposition of the cyanate by alkali is much slower than by acid, and hence this product accumulates in the solution ; while at the same time, especially if the alkali is strong, a certain amount of direct saponification of the urea takes place.

The alkyl ureas exhibit the same phenomena, but in this case the formation of cyanate is more rapid, and a larger amount of this accumulates, so that the results are more complicated.

When urea is strongly heated, it breaks up with the formation of ammonia, carbon dioxide, biuret, and cyanuric acid :—

$$2\,CO(NH_2)_2 = NH_2{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH_2 + NH_3,$$
$$CO(NH_2)_2 = HN{:}CO + NH_3 :$$

the cyanic acid formed in the latter case polymerizing to cyanuric.

If it is heated with potash it forms mainly potassium cyanate.

If urea nitrate, $CO(NH_2)_2{\cdot}HNO_3$, is treated with concentrated sulphuric acid, it gives nitro-urea, $NH_2{\cdot}CO{\cdot}NH{\cdot}NO_2$, an acid stronger than acetic acid (no doubt

[1] *Z. Ph. Ch.* **41.** 601 (1902) ; *J. C. S.* **1904.** 1581 ; **1905.** 494.

having the iso-nitro form), which on reduction yields amino-urea or semi-carbazide $NH_2 \cdot CO \cdot NH \cdot NH_2$.

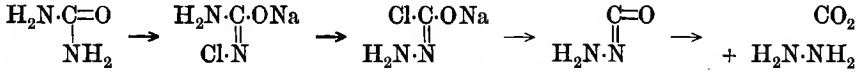
When treated with sodium nitrite or sodium hypobromite it is oxidized to carbon dioxide and nitrogen. Both of these reactions are used for the quantitative estimation of urea, the evolved nitrogen being measured directly. It is to be observed that whereas with hypobromite the nitrogen evolved is that which was contained in the urea:—

$$3\ NaOBr + CO(NH_2)_2 = CO_2 + N_2 + 2\ H_2O + 3\ NaBr,$$

twice this quantity is obtained by the other method, one half coming from the urea and the other half from the nitrous acid:—

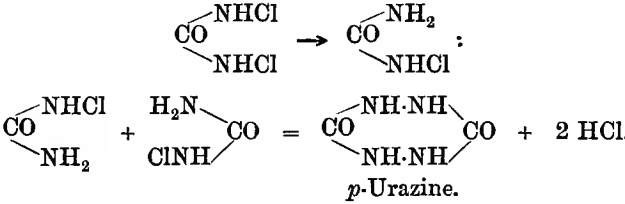
$$CO(NH_2)_2 + 2\ HO \cdot NO = CO_2 + 2\ N_2 + 3\ H_2O.$$

Sodium hypobromite or hypochlorite is also able to act on urea in another way,[1] in accordance with the Hofmann reaction. Urea is an amide, and can therefore give with hypochlorite the corresponding amine and carbon dioxide. The amine formed in this case is hydrazine:—



The amount of hydrazine formed is very small, as it is further oxidized to nitrogen by the excess of hypochlorite. This can to some extent be prevented, and the yield increased, by adding to the solution benzaldehyde, which removes the hydrazine as the comparatively stable benzal-azine $\phi \cdot CH{=}N \cdot N{=}CH \cdot \phi$.

When treated with chlorine in aqueous solution, urea is converted into a symmetrical dichloro-derivative, $CO(NHCl)_2$. This body is broken up by acids with formation of nitrogen chloride, NCl_3, and is converted by ammonia into the so-called diurea or para-urazine. This last reaction probably takes place through the intermediate formation of monochloro-urea[2]:=



p-Urazine.

The alkyl derivatives of urea can be made in various ways:—

1. By Wöhler's method, using mono- or di-alkyl ammonium cyanate; the di-derivatives so formed are of course unsymmetrical.

2. The isocyanic esters give with ammonia monalkyl ureas, with primary and secondary amines symmetrical di- and tri-alkyl ureas:—

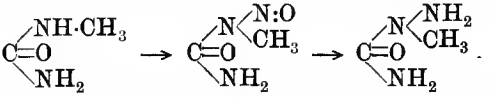


[1] Schestakow, *C.* **05.** i. 1227.

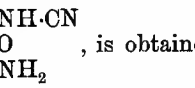
[2] Chattaway, *Chem. News*, **98.** 166 (1908); *J. C. S.* **1909.** 235. Cf. Chattaway, Wünsch, *J. C. S.* **1909.** 129.

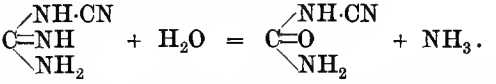
3. The tetra-alkyl derivatives may be obtained by the action of carbonyl chloride on secondary amines.

Those derivatives which no longer contain an NH_2 group can generally be distilled unchanged. Those which contain an NH group yield with nitrous acid nitroso-compounds, which on reduction give semicarbazide derivatives:—

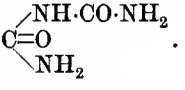


It is interesting to observe that mono-phenyl urea, owing to the negative influence of the phenyl group, will not combine with nitric acid.

Cyan-urea,  , is obtained by treating cyan-guanidine (a polymerization product of cyanamide) with baryta:—



Like nitro-urea it is a strong acid, which expels carbon dioxide from carbonates. When warmed with mineral acids it takes up one molecule of water to form the corresponding amide biuret,



Biuret gives a pink colour when treated with copper sulphate and alkali: this is the so-called biuret reaction which is used as a test for urea and certain amides, such as the polypeptides. It is due to the formation of a copper derivative, in which one of the hydrogen atoms of an NH_2 group is replaced by copper.[1]

The tautomeric form of urea, $HO{\cdot}C{\leqslant}^{NH}_{NH_2}$, the so-called iso-urea, is not known in the free state, but only in certain derivatives. Its methyl ether, $CH_3O{\cdot}C{\leqslant}^{NH}_{NH_2}$, is obtained in the form of its hydrochloride when hydrochloric acid is passed into a solution of cyanamide in methyl alcohol. If this hydrochloride is heated in aqueous solution, it breaks up into methyl chloride and urea.[2] In the analogous case of the O-ethers of the dialkyl-ureas, the velocity of the reaction,

$$Alk_2N{-}C{\leqslant}^{NH_2Cl}_{OCH_3} = Alk_2N{-}C{\leqslant}^{NH_2}_{O} + CH_3Cl,$$

has been measured[3]; and it has been shown that it is probably the undissociated hydrochloride which reacts, and not its ions.

[1] Cf. Schiff, *Ann.* **299.** 236 (1897).
[2] Stieglitz, McKee, *Ber.* **33.** 1517 (1900).
[3] McKee, *Am. Ch. J.* **42.** 1 (*C.* **09.** ii. 1126).

THIO-UREAS

In considering the constitution of the amides it was pointed out that while there is some evidence that they can react in accordance with the isoamide formula $R{\cdot}C\langle^{NH}_{OH}$, yet they must in general be regarded as having the true amide structure $R{\cdot}C\langle^{NH_2}_{O}$. But in the case of the thio-amides there was much stronger evidence for believing that they had the constitution $R{\cdot}C\langle^{NH}_{SH}$. Precisely similar relations hold in the case of the carbonic acid derivatives. Urea itself behaves in accordance with the formula $O{:}C\langle^{NH_2}_{NH_2}$; and there is very little reason for adopting the iso-formula $HO{\cdot}C\langle^{NH}_{NH_2}$. But thio-urea frequently reacts as if it had the formula $HS{\cdot}C\langle^{NH_2}_{NH}$; and though we cannot be certain that the free substance possesses this structure, it must at least be able to assume it in many reactions.

Thio-urea is prepared like urea, by heating ammonium thiocyanate. The change occurs much less readily than in the case of urea, and the proportion of thio-urea present at equilibrium is very much smaller. In order to bring about the change at all rapidly, the dry salt must be heated to 160–170°, and at this temperature equilibrium is reached after about an hour, the amount of thio-urea formed being only 25 per cent. The reaction has been examined by Reynolds and Werner,[1] and more satisfactorily by Findlay.[2] Findlay has determined the freezing-point curve for mixtures of thio-urea and ammonium thiocyanate, and the proportions in the liquid at equilibrium. Ammonium thiocyanate melts at 149°, and thio-urea at a temperature above 177°, which cannot be exactly determined owing to the tautomeric change. The freezing-point curve has the usual form (like that of the benzaldoximes), consisting of two branches meeting at a eutectic point (32 per cent. thio-urea) at 104·3°. The liquid at equilibrium contains 25 per cent. thio-urea, independent of the temperature, showing that the conversion of one form into the other is not accompanied by any appreciable heat effect. This line cuts the thiocyanate branch of the curve at 114–115°, indicating that this is the natural freezing-point, and that the thiocyanate is the stable form. From the fact that the proportions at equilibrium correspond to a compound $CS(NH_2)_2{\cdot}3\ NH_4CNS$, Reynolds and Werner assumed that such a compound was formed; but Findlay has been unable to discover any indications of its existence.

The velocity of the change in the fused substance has been measured by Waddell,[3] who removed portions from time to time and titrated them with silver. He finds the reaction under these conditions (where the ionization is of course very small) to be monomolecular in both directions.

In aqueous solution, ammonium thiocyanate has even less tendency to go over into thio-urea than it has in the case of the melted salt. Dutoit and Gagnaux[4] find that at 140–170° a decinormal solution of ammonium thiocyanate

[1] *J. C. S.* **1903**. 1. [2] Ib. **1904**. 403. [3] *J. Phys. Chem.* **2**. 525 (1898).
[4] *J. Chim. Phys.* **4**. 268 (*C.* **06**. ii. 675).

forms no urea at all, while the reverse change is complete. This latter change (of thio-urea into the thiocyanate) was found to be monomolecular, like that of urea into ammonium cyanate, and to be retarded by the presence of soda but hastened by that of sulphuric acid.

Thio-urea can also be obtained from cyanamide by the action of hydrogen sulphide in the presence of a little ammonia:—

$$H_2N{\cdot}C{\equiv}N + H_2S = S{=}C\begin{matrix}NH_2\\NH_2\end{matrix}.$$

Thio-urea is a crystalline substance, which melts if rapidly heated at about 172°; its true melting-point cannot be determined, owing to the tautomeric change. It sublimes in vacuo at 160°, condensing as ammonium thiocyanate. It forms a comparatively stable salt with hydrochloric acid.[1] Its aqueous solution reacts with mercuric oxide in the cold to give cyanamide. If it is treated with cold permanganate solution, it is converted into urea. When oxidized in acid solution it gives salts of an unstable disulphide

$$H_2N{-}\underset{\underset{NH}{\|}}{C}{-}S{-}S{-}\underset{\underset{NH}{\|}}{C}{-}NH_2.$$

This reaction is a strong argument in favour of the formula $HS{\cdot}C\begin{matrix}NH\\NH_2\end{matrix}$.

The alkyl derivatives of thio-urea are of two kinds, one having the alkyl attached to sulphur, and the other to nitrogen. The mono-, di-, and tri-N-esters may be regarded as derived from either pseudo-form; the S-esters must of course be derived from the imide (iso-) structure.

The N-esters are obtained by the action of ammonia or amines on the isothiocyanic esters or mustard oils:—

$$S{=}C{=}N{\cdot}C_2H_5 + H_2N{\cdot}CH_3 = S{=}C\begin{matrix}NHC_2H_5\\NHCH_3\end{matrix}.$$

It is found that in this reaction the same product is formed from the methyl ester and ethylamine. This has been used as an argument against the imide formula, but it is not of much force. If the body contained an SH group, we should expect ethyl isothiocyanate and methylamine to give $HS{\cdot}C\begin{matrix}NC_2H_5\\NH{\cdot}CH_3\end{matrix}$, while the methyl ester and ethylamine should give $HS{\cdot}C\begin{matrix}NCH_3\\NH{\cdot}C_2H_5\end{matrix}$. But these bodies, differing only in the position of a hydrogen atom, would obviously change into one another with the utmost ease.

Symmetrical diphenyl-thio-urea (thiocarbanilide) is readily obtained by the action of carbon bisulphide on aniline:—

$$C\begin{matrix}S\\S\end{matrix} + \begin{matrix}H_2N\phi\\H_2N\phi\end{matrix} = S{=}C\begin{matrix}NH\phi\\NH\phi\end{matrix} + H_2S.$$

This reaction is characteristic of the aromatic amines, the fatty (and under certain conditions the aromatic also: see p. 183) giving salts of dithiocarbamic acid.

The preparation of thiocarbanilide requires several hours boiling; but it may be much shortened by the addition of certain catalytic agents. For this purpose

[1] *J. C. S.* **1902**. 79.

powdered potash is sometimes used: or a few grams of sulphur may be dissolved in the carbon bisulphide, when the reaction is complete in about an hour. Hydrogen peroxide has a similar effect.[1] The reaction fails unexpectedly in the case of certain amines; but no regularities in this have been observed.

The mixed symmetrical di-derivatives of thio-urea of the type $S{=}C\begin{smallmatrix}NH\cdot C_6H_4X\\NH\cdot C_6H_5\end{smallmatrix}$ when heated are partially converted by a reversible reaction into a mixture of the two simple di-derivatives $SC(NH\phi)_2$ and $SC(NH\cdot C_6H_4X)_2$ (where X = CH_3, NO_2, &c.). This is obviously due to their breaking up into amine and mustard oil, which then recombine.[2]

The N-substituted thio-ureas on treatment with mercuric oxide behave differently according as they do or do not contain an intact NH_2 group. If they do, they lose hydrogen sulphide and form cyanamide derivatives:—

$$S{=}C\begin{smallmatrix}NH\cdot CH_3\\NH_2\end{smallmatrix} + HgO = HgS + H_2O + C\begin{smallmatrix}NH\cdot CH_3\\\equiv N\end{smallmatrix}.$$

If they do not, they merely have the sulphur replaced by oxygen. Thus thiocarbanilide when boiled with mercuric oxide in alcoholic solution gives carbanilide or symmetrical diphenyl-urea:—

$$S{=}C\begin{smallmatrix}NH\phi\\NH\phi\end{smallmatrix} + HgO = O{=}C\begin{smallmatrix}NH\phi\\NH\phi\end{smallmatrix} + HgS.$$

It is, however, possible to bring about a change of the first kind, the removal of hydrogen sulphide, with thiocarbanilide, by boiling it in benzene solution with mercuric oxide. The product is then a derivative of the pseudo-form of cyanamide, carbodiimide:—

$$S{=}C\begin{smallmatrix}NH\phi\\NH\phi\end{smallmatrix} + HgO = C\begin{smallmatrix}N\phi\\\equiv N\phi\end{smallmatrix} + HgS + H_2O.$$

The S-derivatives of thio-urea are obtained as hydriodides by treating thio-urea with alkyl iodide:—

$$S{=}C\begin{smallmatrix}NH_2\\NH_2\end{smallmatrix} + C_2H_5I = C\begin{smallmatrix}{=}NH\\S\cdot C_2H_5\cdot HI\\NH_2\end{smallmatrix}.$$

On treatment with alkali or silver oxide the free thioether is obtained. It is a strongly basic substance, whose structure is shown by its giving a mercaptan on saponification, and a sulphonic acid on oxidation.

The formation of these S-derivatives, which are known as pseudo-thio-ureas, is an argument in favour of the imide formula of thio-urea. Similar compounds[3] are produced by the action of the esters of chlorocarbonic acid, or of acid chlorides, on thio-urea. Thus acetyl chloride gives a compound $C\begin{smallmatrix}{=}NH\\S\cdot CO\cdot CH_3\\NH_2\end{smallmatrix}$. These bodies are somewhat unstable, and if their hydrochlorides are heated, the acyl group migrates to the nitrogen, giving an acyl thio-urea, such as

$$C\begin{smallmatrix}NH\cdot CO\cdot CH_3\\{=}S\\NH_2\end{smallmatrix}.$$

[1] v. Braun, Beschke, *Ber.* **39**. 4369 (1906). [2] Hugershoff, *Ber.* **36**. 1138 (1903).
[3] A. E. Dixon, Hawthorne, *J. C. S.* **1907**. 122.

The derivatives of *carbodiimide*, the diimide of carbonic acid HN=C=NH, are not of great importance. This formula is tautomeric with that of cyanamide, and therefore the monalkyl cyanamides might be supposed to be mono-substitution products of carbodiimide. The evidence, however, is in favour of the true cyanamide formula for these compounds, which will therefore be dealt with among the cyanogen derivatives.

But there are a few bodies which undoubtedly possess this structure. One of these has just been mentioned, and it is typical of the class. They are formed, but only in certain cases, by the action of mercuric oxide on symmetrical di-derivatives of thio-urea. Thus dipropyl urea yields the compound $C_3H_7N{=}C{=}NC_3H_7$. This is the only known alkyl-carbodiimide; and in the aromatic series only a few have been prepared. The diphenyl compound $C(=N\phi)_2$, obtained from thiocarbanilide, can be distilled under 31 mm. pressure at 218°. The distillate forms a glassy mass which, by treatment with boiling ligroin, can be divided into two parts, a soluble oil and an insoluble powder melting at 158–160°. These two substances have the same composition, and their chemical behaviour is identical. They are possibly stereoisomers, since the body contains two N=C groups.

This substance is characterized, as one would expect, by a strong tendency to form addition-compounds. When treated with alcohol and hydrochloric acid it takes up water to give carbanilide $CO(NH\phi)_2$. It combines with hydrogen sulphide at the ordinary temperature to give thiocarbanilide, with aniline to give triphenyl-guanidine:—

$$C\begin{matrix}N\phi\\N\phi\end{matrix} + H_2N\phi = C\begin{matrix}N\phi\\NH\phi\\NH\phi\end{matrix}:$$

and with carbon bisulphide at 140° to give phenyl mustard oil (isothiocyanate):—

$$C\begin{matrix}N\phi\\N\phi\end{matrix} + C\begin{matrix}S\\S\end{matrix} = C\begin{matrix}N\phi\\S\end{matrix} + C\begin{matrix}S\\N\phi\end{matrix}.$$

With phenol and nitrophenol it forms an ether of iso-urea:—

$$C\begin{matrix}N\phi\\N\phi\end{matrix} + \phi{\cdot}OH = C\begin{matrix}N\phi\\O\phi\\NH\phi\end{matrix}.$$

But it is remarkable that 2,4-dinitrophenol and picric acid add on in a different way, forming a normal urea derivative[1]:—

$$C\begin{matrix}N\phi\\N\phi\end{matrix} + HO{\cdot}C_6H_2(NO_2)_3 = C\begin{matrix}NH\phi\\O\\N\phi\\C_6H_2(NO_2)_3\end{matrix}.$$

In all these reactions carbodiphenyl-imide shows a close analogy to an isocyanate, both containing the group $>C{=}N{-}Ar$; and this analogy extends to their polymerization products, the diimide giving a melamine, i. e. a derivative of the amide of cyanuric acid.

[1] Busch, Blume, Pungs, *J. pr. Ch.* [2] **79**. 513 (1909).

GUANIDINE DERIVATIVES

Guanidine, $C(=NH)(NH_2)_2$, is the amidine of carbamic acid. The name was given to it by its discoverer, Strecker, who prepared it in 1861 from guanine, a naturally occurring substance of the uric acid group.

Its constitution is shown by a variety of syntheses. It is formed by the action of ammonia on carbonyl chloride, orthocarbonic ester $C(OC_2H_5)_4$, chloropicrin CCl_3NO_2, or cyanogen iodide. One method of preparation which illustrates its structure peculiarly well is by heating an alcoholic solution of cyanamide with ammonium chloride:—

$$C{\equiv}N(NH_2) + NH_3 = C(=NH)(NH_2)_2.$$

The method adopted in practice for preparing guanidine is to heat ammonium thiocyanate to 180–185° for twenty hours, when ammonium trithiocarbonate, $(NH_4)_2CS_3$, sublimes, and nearly pure guanidine thiocyanate remains behind. The reaction probably proceeds in several stages. Thio-urea is first formed, and this breaks up at the high temperature into hydrogen sulphide and cyanamide. The latter combines with ammonium thiocyanate to form guanidine thiocyanate:—

$$C{\equiv}N(NH_2) + NH_4CNS = C(=NH\cdot HCNS)(NH_2)_2,$$

while the hydrogen sulphide combines with more ammonium thiocyanate to give the trithiocarbonate:—

$$NH_4\text{-}S\text{-}C{\equiv}N + 2\,H_2S = NH_4\text{-}S\text{-}\underset{\displaystyle S}{\overset{\displaystyle \|}{C}}\text{-}S\text{-}NH_4.$$

Free guanidine is a colourless mass, strongly basic and very caustic. It deliquesces in the air, and rapidly absorbs carbon dioxide from it. It forms stable salts with one equivalent of acid, which are mostly soluble, except the nitrate, which, like urea nitrate, is comparatively insoluble.

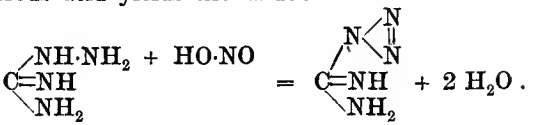
As the imide of urea it is converted into urea on treatment with baryta.

If its hydrochloride is heated to 180° it gives off ammonia and forms biguanide (corresponding to biuret):—

$$2\,C(=NH)(NH_2)_2 = HN(C(=NH)(NH_2))_2 + NH_3.$$

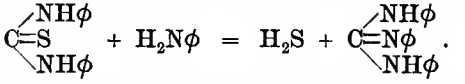
On treatment with fuming nitric acid guanidine is converted into nitroguanidine, $C(=NH\cdot NO_2)(NH_2)_2$, a feebly acid substance which can be reduced first to nitroso- and then to amino-guanidine, $C(=NH\cdot NH_2)(NH_2)_2$. This substance when

treated with nitrous acid yields the azide:—

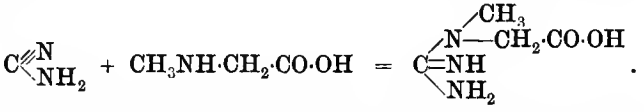


In accordance with this formula it breaks up when treated with alkali into cyanamide and hydrazoic acid HN_3.

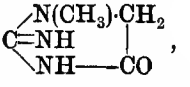
The substituted (alkyl or aryl) guanidines may be obtained by acting on cyanamide with amine hydrochlorides instead of ammonium chloride. Symmetrical triphenyl guanidine, $\phi N{:}C(NH\phi)_2$, is formed as a by-product in many reactions in which the main product is symmetrical diphenyl urea or a similar substance. Thus it is formed in the preparation of thiocarbanilide:—



There are two guanidine derivatives which are of great physiological importance, creatin and creatinin. Creatin occurs in the muscles of mammalia, a full-grown man containing about 90 grams. It can be synthesized by the action of sarcosin (methyl-amino-acetic acid) on cyanamide, whereby its formula is established:—



On boiling with water, especially in presence of acids, it loses water and goes over into its cyclic amide, creatinin:—



a substance which occurs to a small extent in urine.

CHAPTER IX

CYANOGEN COMPOUNDS

The derivatives of cyanogen may be classified as follows :—

I. The cyanides and isocyanides, R–C≡N and R–N≡C or R–N=C.

II. The compounds containing the group –(CNO). Of this group four isomeric arrangements are possible, and representatives of all of them are actually known :—

1. The cyanates R–O–C≡N.

2. The isocyanates R–N=C=O.

3. The fulminates, R–O–N=C, which are the esters of the oxime of carbon monoxide.

4. The nitrile-oxides $\begin{matrix} R\cdot C{=}{=}N \\ \diagdown\!O\!\diagup \end{matrix}$.

In the first two of these groups the oxygen may be replaced by sulphur, giving the thiocyanates, R–S–C≡N, and the isothiocyanates or mustard oils, R–N=C=S.

III. The tricyanogen derivatives. All the above-mentioned classes of compounds readily form triple polymers containing the so-called tricyanogen ring



The first of the cyanogen compounds to be prepared was Prussian blue, which was discovered by Diesbach at the beginning of the eighteenth century; but our real knowledge of their constitution dates from the work of Gay-Lussac in 1815. Gay-Lussac showed that these bodies contain a radical composed of carbon and nitrogen, which plays the part of an element. This radical, which may be written –C≡N, –N≡C, or –N=C″, resembles the halogens, especially in forming a hydracid, and in the fact that the molecule of the free substance consists of two such groups joined together, CN–CN being analogous to Cl–Cl.

CYANOGEN $(CN)_2$.

Cyanogen is generally said to be formed by passing the electric arc between carbon poles in an atmosphere of nitrogen. It has however been shown that it cannot be prepared in this way. It follows from Nernst's theorem that a considerable percentage of cyanogen must be formed at a temperature of 3,500°, but it is apparently all decomposed in passing out of the arc.[1] It is usually prepared by heating mercuric cyanide, by which method it was first obtained by Gay-Lussac in 1815. Another method of making it is by the action of potassium

[1] Berthelot, *C. R.* **144.** 354 (1907); Wallis, *Ann.* **345.** 353 (1907); Wartenberg, *Z. an. Ch.* **52.** 299 (*C.* **07.** i. 800).

cyanide on copper sulphate in solution. Cupric cyanide, or a double compound of this with potassium cyanide, is first formed; but on heating the solution this breaks up into cuprous cyanide and cyanogen which is evolved. It is also contained in coal gas, along with prussic acid, in sufficient quantity to supply the whole commercial demand for cyanogen compounds; and a proposal has been made[1] to utilize this source by passing the gas through a mixture of a ferrous salt and lime, when the cyanogen is obtained as calcium ferrocyanide. It has further been proposed to make it on the large scale by passing nitrogen over iron covered with coke (and therefore saturated with carbon) at 1,500–1,800°.[2]

There are three possible formulae for cyanogen :—

$$\begin{array}{l} C{\equiv}N \\ | \\ C{\equiv}N \end{array}' \qquad \begin{array}{l} N{=}C \\ | \\ N{=}C \end{array}' \qquad \begin{array}{l} C{\equiv}N \\ | \\ N{=}C \end{array}.$$

Cyanogen is the only known substance of the molecular formula C_2N_2, and it is proved to have the first of these structures by its formation from ammonium oxalate or oxamide on treatment with phosphorus pentoxide :—

$$\begin{array}{l} O{=}C\text{–}NH_2 \\ | \\ O{=}C\text{–}NH_2 \end{array} - 2\,H_2O = \begin{array}{l} C{\equiv}N \\ | \\ C{\equiv}N \end{array},$$

and from glyoxime (the oxime of glyoxal) on treatment with acetic anhydride :—

$$\begin{array}{l} H\text{–}C{=}NOH \\ | \\ H\text{–}C{=}NOH \end{array} - 2\,H_2O = \begin{array}{l} C{\equiv}N \\ | \\ C{\equiv}N \end{array}.$$

Both of these reactions show that the two carbon atoms are linked together.

Cyanogen is a colourless gas of a peculiar smell; it boils at −20·7° and melts at −34·4°. It is extremely poisonous. It is very stable to heat, not being affected even at 800°; above that temperature it slowly breaks up. Liquid cyanogen has a very low electric conductivity, and practically no dissociating power.[3] Cyanogen gas burns with a characteristic purple-mantled flame. One volume of water dissolves four volumes of the gas, one volume of alcohol twenty-three.[4] If the saturated aqueous solution is left in contact with the gas, it continues to absorb it slowly, as cyanogen is unstable in solution, and at once begins to decompose, depositing a brown amorphous mass known as azulmic acid, while the solution contains ammonium oxalate, ammonium carbonate, prussic acid, and urea.

As the nitrile of oxalic acid cyanogen is saponified by fuming hydrochloric acid or by hydrogen peroxide to oxamide; and like chlorine it is absorbed by aqueous potash to give a mixture of the cyanide and cyanate :—

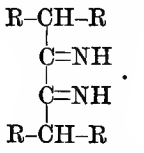
$$(CN)_2 + 2\,KOH = KCN + KCNO + H_2O.$$

In the presence of a trace of sodium ethylate, cyanogen is able to add itself on to compounds containing an acidic methylene group.[5] Thus with acetoacetic ester it gives at low temperatures a body

$$CH_3{\cdot}CO{\cdot}\begin{array}{l} CH{\cdot}COOEt \\ | \\ C{=}NH \\ | \\ C{\equiv}N \end{array},$$

[1] Feld, Nauss, *C.* **03.** i. 264.
[2] Erlwein, *C.* **08.** ii. 273.
[3] Centnerszwer, *Z. Ph. Ch.* **39.** 217 (1901).
[4] Berthelot, *C.* **04.** ii. 428.
[5] W. Traube, *Ber.* **31.** 191, 2938 (1898).

while at higher temperatures one molecule of cyanogen reacts with two molecules of the methylene compound, giving bodies of the type



Paracyanogen, a polymer of cyanogen of unknown molecular weight, is formed as a by-product in the preparation of cyanogen by heating mercuric cyanide, and is the form in which the whole of the cyanogen is obtained when an aqueous solution of potassium cyanide is electrolysed. It is a brown amorphous insoluble powder, which is reconverted into cyanogen gas at 860°.

HYDROCYANIC ACID

The simplest derivative of cyanogen is hydrocyanic or prussic acid, whose formula is either H–C≡N or H–N=C″. It is a tautomeric substance: that is to say it gives rise to derivatives of both forms. It is an extremely complicated question which of these two formulae is to be adopted for the acid and for its salts; and as its solution depends on a comparison of their properties with those of the organic derivatives—the nitriles and the isocyanides—the discussion will be deferred until these bodies have been considered.

Prussic acid occurs in nature in the glucoside amygdalin, which is contained in bitter almonds, and when it is hydrolysed—which can be done by means of a ferment also contained in the almonds—splits up into prussic acid, benzaldehyde, and sugar. In the free state it is found in the tree *Pangium edule* which grows in Java. All parts of this tree contain free prussic acid, but particularly the seeds; and it is calculated that a full-grown tree contains at least 350 grams.

It has recently been shown[1] that prussic acid is much more widely distributed in the vegetable world than had previously been supposed, occurring mainly in the form of glucosides. There is some reason to think that it may be produced by the action of the carbohydrates on the inorganic nitrates, whose presence can often be detected in those plants which yield prussic acid.[2]

Prussic acid was discovered by Scheele in 1782, and was first obtained in the anhydrous state by Gay-Lussac in 1811. It is formed by the combination of hydrogen and cyanogen at high temperatures, or under the influence of the silent electric discharge; or by passing sparks through a mixture of nitrogen or ammonia and acetylene, or of carbon monoxide, nitrogen, and hydrogen.[3] It can also be made[4] by passing a carefully dried mixture of hydrogen, ammonia, and a volatile carbon compound (such as carbon monoxide,

[1] Arragon, Guignard, *C.* **06.** ii. 1849; cf. Greshoff, *Arch. der Pharm.* **244.** 397 (1906 Couperot, *C.* **09.** i. 387.

[2] Ravenna, Peli, *C.* **08.** i. 654; cf. Plimmer, *C.* **05.** i. 357.

[3] Gruszkiewicz, *Z. f. Elektrochem.* **9.** 83 (*C.* **03.** i. 494); Hoyermann, *C.* **02.** i. 525; Briner, Durand, *J. Chim. Phys.* **7.** 1 (*C.* **09.** i. 1453).

[4] Woltereck, *C.* **04.** i. 1306.

carbon dioxide, acetylene, or the vapour of alcohol or petroleum) over heated platinized pumice; and this method has been used for making it on the large scale. It is formed when ammonia comes in contact with red-hot carbon, as in the manufacture of coal-gas, the conversion being complete at 1300°; and by the action of a high temperature on many nitrogenous substances containing carbon: thus it has been found [1] in cigar smoke to the extent of one milligram to every 4 or 5 (Austrian) cigars. Its salts are produced when organic nitrogenous substances are raised to a high temperature in contact with potassium or sodium, or when metallic nitrates are heated with charcoal in closed vessels.[2] It is also formed from many phenols (especially nitrophenols) and similar compounds by boiling with dilute nitric acid.[3]

Prussic acid is usually prepared by the action of dilute sulphuric acid on potassium ferrocyanide:—

$$3\,H_2SO_4 + 2\,K_4FeCy_6 = 3\,K_2SO_4 + K_2Fe{\cdot}FeCy_6 + 6\,HCN.$$

It is also produced by the dry distillation of ammonium formate:—

$$H\text{-}C\begin{matrix}\nearrow O\\ \searrow O\text{-}NH_4\end{matrix} = 2\,H_2O + H\text{-}C{\equiv}N,$$

which has been used as an argument for the nitrile formula: and by the action of chloroform and ammonia on alcoholic potash:—

$$CHCl_3 + NH_3 + 3\,KOH = H\text{-}N{=}C + 3\,KCl + 3\,H_2O,$$

which is an equally weak argument in favour of the isocyanide formula.

Hydrocyanic acid is a colourless liquid with a smell like bitter almonds. It is remarkable that different people differ more in their power of detecting this smell than any other. It burns with a violet flame. It is one of the most powerful of poisons; the best antidote to it is either hydrogen peroxide, or inhaling air containing chlorine.

Liquid prussic acid has a very high dielectric constant,[4] higher indeed than that of water; in this it resembles the nitriles, for which also the values of this constant are high, though not so high. It also, as we should expect from this, has a high dissociating power [5]; and some salts, such as potassium iodide, conduct better in prussic acid than in water. Cryoscopic measurements have also shown that these salts are practically completely dissociated in this solvent, while acids (such as trichloracetic and sulphuric) give normal values and appear not to dissociate at all.[6]

It has been shown by Nef [7] that anhydrous prussic acid as usually prepared contains a small quantity of ammonium cyanide, by which its properties are sensibly modified. If the liquid is allowed to stand over phosphorus pentoxide, and then distilled through tubes containing phosphorus pentoxide and warmed to 40–50°, a pure acid is obtained. This boils at 25°, and solidifies on cooling to a colourless crystalline mass melting at −10° to −12°. When completely

[1] Habermann, *C.* **03.** i. 53. [2] Müller, *C.* **08.** i. 1343.

[3] Seyewetz, Poizat, *C. R.* **148.** 286, 1110; *Bull. Soc.* [4] **5.** 489 (*C.* **09.** i. 997).

[4] Schlundt, *J. Phys. Chem.* **5.** 157 (*C.* **01.** i. 1135).

[5] Centnerszwer, *Z. Ph. Ch.* **39.** 220 (1901); Kahlenberg, Schlundt, *J. Phys. Chem.* **6.** 447 (*C.* **03.** i. 1).

[6] Lespieau, *C. R.* **140.** 855 (1905). [7] *Ann.* **287.** 327 (1895).

purified in this way prussic acid is an extraordinarily stable substance. It may be kept for months in sealed tubes without change, and it is not acted on at $-10°$ by chlorine, hydrochloric acid, or ethyl hypochlorite. If the acid contains traces of impurity, such as water or potassium cyanide, it rapidly turns brown, forming the so-called azulmic compounds, about which very little is known. The aqueous solution rapidly decomposes, especially if exposed to light, forming a brown precipitate of azulmic acid, while ammonia, formic and oxalic acids, and other substances remain in solution. In the presence of a trace of mineral acid the aqueous solution is more stable.

On reduction prussic acid yields methylamine. If it is hydrolysed with concentrated aqueous hydrochloric acid it gives formamide, while an alcoholic solution of hydrochloric acid converts it into esters of formic acid. These reactions are equally consistent with either of the two formulae.

It reacts with diazomethane, and according to v. Pechmann the product is methyl cyanide:—

$$CH_2\begin{matrix}\diagup N \\ \| \\ \diagdown N\end{matrix} + H{-}C{\equiv}N = CH_3{\cdot}C{\equiv}N + N_2.$$

This is commonly regarded as a strong argument for the nitrile formula, since diazomethane is a general reagent for replacing hydrogen by methyl, and especially since the reaction goes on at a low temperature. But it has recently been found that methyl isocyanide is formed at the same time, which destroys the force of this argument; and indeed the nitrile itself is at least as likely to be formed from H–N=C, as will be shown later.

Owing no doubt to its highly unsaturated character, prussic acid has a great power of forming addition-compounds. Thus it combines with hydrochloric acid in ethyl acetate solution, giving a body of the composition 2HCN·3HCl. The formula of this substance has been shown to be

$$H{-}C\begin{matrix}\diagup NH \\ \diagdown NH{\cdot}CHCl_2\end{matrix}, HCl.$$

It is dichlormethyl-formamidine hydrochloride. This is proved by its giving with alcohol formamidine:—

$$H{\cdot}C\begin{matrix}\diagup NH \\ \diagdown NH{\cdot}CHCl_2\end{matrix} + 2\,EtOH = 2\,EtCl + CH_2O_2 + H{\cdot}C\begin{matrix}\diagup NH \\ \diagdown NH_2\end{matrix},$$

and further by its reacting readily with benzene and aluminium chloride to give diphenyl-formamidine:—

$$H{\cdot}C\begin{matrix}\diagup NH \\ \diagdown NH{\cdot}CHCl_2\end{matrix} + 2\,C_6H_6 = H{\cdot}C\begin{matrix}\diagup NH \\ \diagdown NH{\cdot}CH\phi_2\end{matrix} + 2HCl.$$

Hydrocyanic acid can also form a simpler compound with hydrochloric acid, imino-formyl chloride, $Cl{\cdot}C\begin{matrix}\diagup NH \\ \diagdown H\end{matrix}$. This body cannot be isolated, but its formation is proved by Gattermann's reaction for the synthesis of aldehydes.[1] If an aromatic hydrocarbon or a phenol or a phenol ether is treated with prussic acid and hydrochloric acid, either alone, or in presence of a condensing agent such as zinc chloride or aluminium chloride, it is converted into an aldimine, from

[1] *Ber.* **31.** 1149, 1765 (1898); *Ann.* **347.** 347 (1906); **357.** 313 (1907).

which the aldehyde is easily obtained by heating with dilute acid. This can only be explained by the intermediate formation of the imino-formyl chloride:—

$$C_6H_6 + Cl{\cdot}C\langle{}^{NH}_{H} = HCl + C_6H_5{\cdot}C\langle{}^{NH}_{H} \longrightarrow NH_3 + C_6H_5{\cdot}C\langle{}^{O}_{H}.$$

Prussic acid will combine with aldehydes and ketones to form the so-called cyanhydrins, which are really the nitriles of the α-oxy-acids:—

$$(CH_3)_2C{=}O + HCN = (CH_3)_2C\langle{}^{OH}_{CN}.$$

A reaction which very probably depends on the formation of a cyanhydrin is the benzoin synthesis. If benzaldehyde is heated in alcoholic solution with a small quantity of potassium cyanide, it is converted into benzoin:—

$$\phi{\cdot}CHO + OHC{\cdot}\phi = \phi{\cdot}CHOH{\cdot}CO{\cdot}\phi.$$

The same reaction occurs with many aromatic aldehydes (including furfurol), but it does not take place in the fatty series. The action of the potassium cyanide is catalytic: that is to say, it does not appear in the equation, and a small quantity of it can effect a large amount of the reaction. The dynamics of this change have been investigated by Stern.[1] The reaction was carried out in sealed tubes at 60°, in 60 per cent. aqueous alcohol. In order to determine the amount of change after a given time, the reaction was stopped by acidifying the solution, the prussic acid and benzaldehyde were distilled off with steam, and the benzoin was estimated with Fehling's solution. It was found that with a constant quantity of the catalytic agent, the rate of formation of benzoin was proportional to the square of the concentration of the benzaldehyde, as we should expect from the equation. If the amount of potassium cyanide is varied, the bimolecular constant varies in proportion to it. Sodium or barium cyanide has practically the same effect as potassium cyanide; prussic acid itself does not bring about the synthesis at all. This shows that the reaction depends on the cyanogen ion. This was further proved by the fact that if silver or mercuric cyanide is added as well as potassium cyanide, the constant obtained is the same as that calculated for the excess of potassium cyanide after subtracting the amount required for the complete formation of the double cyanide of potassium and silver or potassium and mercury; in other words, the part of the cyanogen ion which has gone over into the complex ion has no influence.

The reaction is hastened by increasing the proportion of water in the solvent.

Various theories as to the mechanism of this reaction have been suggested; those which ascribe it either to prussic acid or to hydroxyl ion are shown by these experiments to be untenable. It is certainly due to the potassium cyanide, or to the cyanogen ion. The suggestion which best agrees with the facts is that of Chalanay and Knoevenagel.[2] They suppose that three successive reactions take place:—

(1) $$\phi{\cdot}C\langle{}^{H}_{O} + KCN = \phi{\cdot}C\langle{}^{K}_{O} + HCN,$$

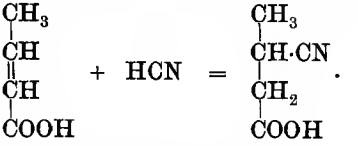
(2) $$\phi{\cdot}C\langle{}^{H}_{O} + HCN = \phi{\cdot}CH\langle{}^{OH}_{CN},$$

(3) $$\phi{\cdot}CH\langle{}^{OH}_{CN} + \phi{\cdot}C\langle{}^{K}_{O} = KCN + \phi{\cdot}CHOH{\cdot}CO{\cdot}\phi.$$

[1] *Z. Ph. Ch.* **50**. 513 (1905). [2] *Ber.* **25**. 295 (1892).

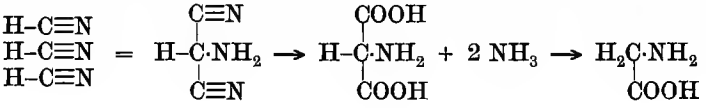
If we assume that reactions (1) and (2) are very rapid, and that the quantity of the intermediate products formed is very small, it can easily be shown that the rate of formation of benzoin is proportional to the concentration of the potassium cyanide, and to the square of the concentration of the benzaldehyde.

Prussic acid can add on to the grouping C=C, but with much less ease than to the grouping C=O, and only in particular cases; whereas sulphurous acid combines with either of these groups with equal ease. An example is the formation of nitrile-acids from certain unsaturated acids:—



As this reaction is greatly hastened by the presence of primary or secondary bases, it is probably due to the cyanogen ion.[1]

If an aqueous solution of prussic acid, containing a little potassium carbonate, is allowed to stand, it deposits azulmic acid; and if it is now extracted with ether, the ether is found to contain a polymer of prussic acid. This substance on saponification with acid or alkali yields carbon dioxide, ammonia, and glycocoll. It is, therefore, probably the nitrile of amino-malonic acid:—



Salts of Prussic Acid

Prussic acid is a distinct acid, though a very weak one. Its dissociation constant ($K = 0{\cdot}0013 \times 10^{-6}$) is less than a ten-thousandth of that of acetic acid ($18{\cdot}0 \times 10^{-6}$). It turns litmus a dark red, and forms salts, which, however, are decomposed by carbonic acid. The salts of the alkalies and alkaline earths are soluble in water, have an alkaline reaction, and are stable even at a red heat. The salts of the heavy metals on the other hand are insoluble (except mercuric cyanide), are not decomposed by any but strong acids, and break up at a red heat into the metal and cyanogen. Mercuric cyanide has a remarkable behaviour, owing to the fact that while it is soluble in water it is not ionized to a perceptible extent, so that it is scarcely correct to call it a salt. Its solution does not conduct electricity, and does not give the ordinary tests for mercury or for a cyanide; it gives no precipitate either with silver nitrate or with alkali.[2]

The cyanides of the heavy metals all dissolve in potassium cyanide with the formation of double cyanides. Many of these double cyanides do not give the reactions either of cyanides or of the heavy metals which they contain. The ferro- and ferricyanides, for example, are scarcely poisonous: on treatment with acids in the cold they liberate ferro- and ferricyanic acids, H_4FeCy_6 and H_3FeCy_6; and the iron is not precipitated by alkali or alkaline sulphide. All these facts

[1] Knoevenagel, *Ber.* **37**. 4065 (1904).

[2] It is, however, capable under certain conditions of giving tests for these ions. See Hofmann, Wagner, *Ber.* **41**. 317 (1908). Cf. Borelli, *Gaz.* **38**. i. 361 (*C.* **08**. ii. 288).

indicate that the iron is not present as cation but as part of the anion—of the complex acid radical. Hence the ordinary tests for cyanion and for ferro- and ferri-ion fail, because the solution does not contain these ions (to a measurable extent), but only $K^{\cdot}$ and $FeCy_6'''$ or $FeCy_6''''$.

The double cyanide of potassium and silver, $KAgCy_2$, is much used in commerce, being the only soluble silver compound which gives satisfactory results in silver plating. The reason for this is interesting. The only way to obtain an electrolytic deposit of silver of the proper consistency is to employ a bath in which the concentration of silver ions is very small. This condition might be secured by using silver nitrate, if the solution were made sufficiently dilute; but since silver nitrate is practically completely dissociated, the concentration would have to be almost infinitesimal, and this would cause the bath to have an enormous resistance and the electrolysis to go on very slowly. But potassium argenticyanide, when dissolved in water, breaks up almost entirely into the ions $K^{\cdot}$ and $AgCy_2'$; while to an excessively small extent the latter dissociates further into $Ag^{\cdot}$ and CN'. It is therefore possible by using the double cyanide to obtain a solution which conducts well, and contains a considerable quantity of silver, and yet a very small concentration of silver ions. As fast as the silver is deposited a fresh quantity of silver ions is formed, so as to preserve the equilibrium; and thus the bath does not become exhausted.

If an alternating current is passed through a potassium cyanide solution by means of copper electrodes, the positive current carries copper ions into the solution; these ions combine with the cyanion to form complex anions, from which, therefore, the copper is not deposited by the reverse current; so that the poles dissolve. But if the alternations of the current are very rapid, there is not time for the copper ion to form the complex ion before the reverse current brings it out of solution again. By observing the rate of alternation at which the solution of the electrodes ceases, it is possible to determine the time required for the formation of the complex ion. This is naturally less the more concentrated the potassium cyanide; it lies between $\frac{1}{1000}$ and $\frac{1}{80000}$ of a second.[1]

The reaction between potassium cyanide and hydrogen peroxide has been investigated in detail by Orme Masson,[2] who has shown that it proceeds in two directions. First, the cyanide is oxidized to cyanate, and this is hydrolysed, under the catalytic influence of the peroxide, to ammonia and carbonic acid. At the same time a part of the cyanide is hydrolysed, without oxidation, to ammonia and formic acid. The rate of oxidation is proportional to the product of the concentrations of the peroxide and the cyanide. The most remarkable fact is that the second reaction (the production of formate) always takes place to the same extent, one-fifth of the cyanide being hydrolysed in this way, while four-fifths are oxidized to cyanate.

[1] Le Blanc, Schick, *Z. Ph. Ch.* **46**. 213 (1904); Le Blanc, *Z. Elektrochem.* **11**. 705 (*C.* **05**. ii. 1619); Löb, *Z. Elektrochem.* **12**. 79 (*C.* **06**. i. 728). Cf. also Eucken, *Z. Ph. Ch.* **64**. 562 (1908), who finds the velocity constant for the dissociation of the $AgCy_2'$ ion to be greater than $7{\cdot}5 \times 10^{20}$: that is, if the $AgCy_2'$ ions were maintained at normal concentration, in one second more than $7{\cdot}5 \times 10^{20}$ gr. molecules would dissociate per litre.

[2] *J. C. S.* **1907**. 1449.

NITRILES

Prussic acid, in accordance with its tautomeric character, gives rise to two classes of esters. The normal cyanides or nitriles are derived from the form H–C≡N. They may be regarded either as hydrocarbons in which one hydrogen has been replaced by the monovalent CN group, or as acids in which the carboxyl group has been converted into CN. Accordingly $CH_3 \cdot CN$, for example, may be called methyl cyanide on the analogy of methyl chloride, $CH_3 \cdot Cl$, or acetonitrile, after the acid into which it can be converted.

The nitriles were discovered in 1834, when Pelouze obtained propionitrile by distilling barium ethyl sulphate with potassium cyanide. In 1847 Dumas prepared acetonitrile by the action of phosphorus pentoxide on ammonium acetate. Their reactions were investigated soon after this, mainly by Dumas and by Frankland and Kolbe, who showed that on hydrolysis they yield acids containing the same number of carbon atoms. This reaction establishes their constitution.

Methods of formation

1. From potassium cyanide and alkyl iodide. This generally requires the presence of a solvent. The alkyl iodide is dissolved in aqueous alcohol and the cyanide added. The reaction takes place either in the cold or on warming; a certain amount of isocyanide is formed at the same time. In some cases, as with tertiary butyl iodide, it is better instead of potassium cyanide to use the double cyanide of potassium and mercury.

2. From the salts of the alkyl-sulphuric acids, by distillation with potassium cyanide. Here, too, a little isocyanide is generally formed as a by-product, but it can easily be destroyed by shaking with cold concentrated hydrochloric acid, which immediately hydrolyses the isocyanide, while it leaves the nitrile practically unaffected.

3. From cyanogen chloride and zinc alkyl.

4. By heating the isocyanides to about 250°, when they change over into nitriles.

In all these reactions the carbon chain is lengthened; but there are also a series of methods of formation from the acids, i.e. without altering the carbon chain: —

1. By converting the acid into its amide, and treating this with a dehydrating agent:—

$$R \cdot C\langle^{O}_{ONH_4} \longrightarrow R \cdot C\langle^{O}_{NH_2} \longrightarrow R \cdot C \equiv N.$$

The dehydrating agent usually employed is phosphorus pentoxide; but in some cases it is found better to treat the amide in pyridine solution with carbonyl chloride.[1] The carbonyl chloride seems to act only by removing the elements of water, and the pyridine facilitates the reaction by taking up the hydrochloric acid formed:—

$$R \cdot CO \cdot NH_2 + COCl_2 = R \cdot CN + CO_2 + 2\,HCl.$$

[1] Einhorn, Mettler, *Ber.* **35.** 3647 (1902).

The whole change from acid to nitrile may be carried out in one operation by distilling the acid with potassium thiocyanate:—

$$CH_3{\cdot}COOH + HCNS = CH_3{\cdot}CONH_2 + COS = CH_3{\cdot}CN + H_2S + CO_2.$$

2. By distilling the acids in a stream of ammonia through a red-hot tube. This explains the occurrence of nitriles in animal oil, and of acetonitrile in commercial benzene.

3. From the aldehydes by conversion into aldoximes and dehydration with acetic anhydride:—

$$CH_3{\cdot}CH{:}NOH = H_2O + CH_3{\cdot}CN.$$

Another method by which an acid can be converted into a nitrile—in this case containing an atom of carbon less—is the Hofmann reaction. In this reaction, as has already been explained, the acid is converted into its amide, and this is treated with bromine and potash. This gives primarily an amine with one atom of carbon less than the original acid; but if the amine so formed contains more than four carbon atoms, the bromine and potash act on it further to oxidize it, removing hydrogen, and forming a nitrile:—

$$C_5H_{11}{\cdot}CONH_2 \longrightarrow C_4H_9{\cdot}CH_2{\cdot}NH_2 \longrightarrow C_4H_9{\cdot}CN.$$

This last stage is really a reversal of the Mendius reaction, in which a nitrile is reduced to a primary amine.

In the case of the aromatic compounds, the above methods require to be somewhat modified. Chlorobenzene will only react with potassium cyanide above 300°, and hence this method is not usually adopted for preparing the nitrile. On the other hand benzoic acid, like acetic acid, readily yields its nitrile when treated with potassium or lead thiocyanate; and its amide does so on treatment with carbonyl chloride in the presence of pyridine. But the simplest and most usual method in the aromatic series is one which is not available with the fatty compounds: it consists in treating a diazo-compound with cuprous cyanide:—

$$\phi{\cdot}N_2{\cdot}CN = N_2 + \phi{\cdot}CN.$$

Properties

The lower nitriles are colourless volatile liquids of a not unpleasant smell, which are somewhat soluble in water. They are readily saponified by acids or alkalies to form ammonia and the corresponding acid, a reaction equally important from the theoretical and from the practical point of view. In the aromatic series a somewhat high temperature is required to bring about the change. If the saponification is carried out with an alcoholic solution of hydrochloric or sulphuric acid, the ester is produced.

Kaufler[1] has determined the velocity of hydrolysis of 2,7-dicyan-naphthalene, as an example of the occurrence of two successive similar reactions. He deduces an expression for the amount of change, assuming each reaction to be monomolecular. The dicyanide was heated in amyl alcohol solution with excess of alcoholic potash, and a stream of air passed through; the rate of reaction was

[1] *Z. Ph. Ch.* **55.** 502 (1906).

measured by the amount of ammonia evolved. The results agree fairly well with the theory, the ratio of the two reaction constants being about 6 : 1.

In this saponification the triple link between the carbon and the nitrogen is completely broken; but there are many reactions in which it is only partially destroyed. Thus a nitrile can take up one molecule of water to form an amide. This may be brought about by heating it with water to 180°, or with alkaline hydrogen peroxide to 40°. In the latter case, as has been pointed out, oxygen is evolved, and the reaction appears to be due to nascent water:—

$$R{\cdot}CN + H_2O_2 = R{\cdot}CO{\cdot}NH_2 + O.$$

There are many other analogous reactions. If heated with acids the nitriles form secondary amides, and with acid anhydrides, tertiary amides:—

$$CH_3{\cdot}CN + O\langle\begin{matrix}CO{\cdot}CH_3\\CO{\cdot}CH_3\end{matrix} = CH_3{\cdot}CO{\cdot}N\langle\begin{matrix}CO{\cdot}CH_3\\CO{\cdot}CH_3\end{matrix}.$$

Similarly with hydrogen sulphide they give thioamides. With hydrochloric acid they form imino-chlorides, or in alcoholic solution imino-ethers:—

$$CH_3{\cdot}C{\equiv}N + HCl = CH_3{\cdot}C\langle\begin{matrix}Cl\\NH\end{matrix}.$$

With hydrobromic acid a different reaction occurs; two molecules are taken up instead of one, and an amido-bromide is formed:—

$$CH_3{\cdot}C{\equiv}N + 2\,HBr = CH_3{\cdot}C\langle\begin{matrix}Br_2\\NH_2\end{matrix}.$$

Bromine first substitutes in the alkyl group, and then the hydrobromic acid so produced adds on to form an imino-bromide:—

$$C_2H_5{\cdot}C{\equiv}N + Br_2 = C_2H_4Br{\cdot}C{\equiv}N + HBr = C_2H_4Br{\cdot}C\langle\begin{matrix}Br\\NH\end{matrix}.$$

Nascent hydrogen converts the nitriles into amines (Mendius reaction).

Hydroxylamine converts them into amidoximes:—

$$CH_3{\cdot}C{\equiv}N + H_2NOH = CH_3{\cdot}C\langle\begin{matrix}NOH\\NH_2\end{matrix}.$$

This reaction goes peculiarly easily when there are halogen atoms in the nitrile[1]: thus dichlor-acetonitrile forms $CHCl_2{\cdot}C\langle\begin{matrix}NOH\\NH_2\end{matrix}$.

All these reactions are typical of an unsaturated body. They are additive reactions, and, as in all additive reactions, the molecule which is added on divides into two or more parts, which then satisfy one or two of the three links between the carbon and the nitrogen. The position which these groups take up is governed by the respective affinities of the carbon and the nitrogen. Oxygen always tends to attach itself to carbon, and hydrogen to nitrogen.

Another property which the nitriles share with all unsaturated bodies is the tendency to polymerize—that is, to form addition-products with themselves. These polymers can be formed by the combination of either two or three molecules of the same or of different nitriles. The bimolecular compounds are indifferent substances; the trimolecular are strongly basic. They are all formed by the action of sodium on the nitriles under different conditions. In ethereal

[1] Steinkopf, Bohrmann, *Ber.* **40.** 1633 (1907).

solution the bimolecular polymers are obtained; but on treatment with sodium in the absence of a solvent, or on heating with dry sodium ethylate to 140°, the cyanides of primary alcoholic radicals produce the basic trimolecular polymers known as cyanalkines.

The first stage in the formation of these bodies appears to consist in the formation of sodium derivatives of the nitriles. These have only been isolated in the case of certain aromatic compounds, such as benzyl cyanide (phenyl-acetonitrile), $\phi \cdot CH_2 \cdot CN$, where the negative influence of the CN group is strengthened by that of the phenyl. But there is evidence of their existence in the fatty series: as in the production of butyronitrile by the action of sodium on a mixture of acetonitrile and ethyl iodide:—

$$CH_2Na \cdot CN + C_2H_5I = C_2H_5 \cdot CH_2 \cdot CN + NaI.$$

In the production of a double polymer from acetonitrile by treatment with sodium, marsh gas is evolved and sodium cyanide formed. This indicates that one sodium atom turns out a methyl group from one molecule of acetonitrile, forming sodium cyanide, while another displaces a hydrogen from a second molecule to give $CH_2Na \cdot CN$, this hydrogen combining with the methyl to give methane:—

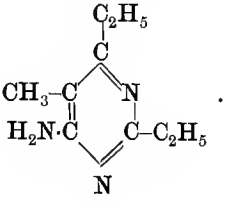
$$2\,Na + 2\,CH_3 \cdot CN = NaCN + CH_4 + CH_2Na \cdot CN.$$

The sodium derivative now combines with another molecule of the nitrile thus:—

$$\begin{array}{rcl} & CH_3 \cdot C{\equiv}N & \\ + & CH_2Na \cdot CN & = \begin{array}{l} CH_3 \cdot C{=}N \cdot Na \\ \quad\quad | \\ \quad CH_2 \cdot CN \end{array} \end{array},$$

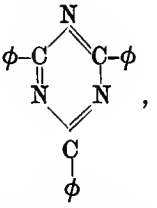
and this on treatment with water yields the hydrogen compound $\begin{array}{l} CH_3 \cdot C{=}NH \\ \quad\quad | \\ \quad CH_2 \cdot CN \end{array}$, which is the imino-nitrile of acetoacetic acid. That this is the structure of the polymer is shown by its hydrolysing with cold acid to the ketone-nitrile, $CH_3 \cdot CO \cdot CH_2 \cdot CN$, and with hot acid (through acetoacetic acid) to carbon dioxide and acetone.[1]

The formation of the trimolecular derivatives or cyanalkines is not understood; but their constitution has been made out, and they are found to be amino-pyrimidine derivatives. Thus cyanethine (from propionitrile) is amino-methyl-diethyl-pyrimidine

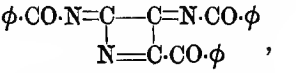


It is remarkable that while the alkyl cyanides give these pyrimidine derivatives, the triple polymer which benzonitrile forms under the same conditions (cyaphenine) has quite a different constitution, being a cyanuric compound with the tricyanogen ring:—

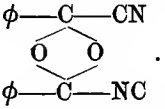
[1] Benzyl cyanide behaves in the same way. Atkinson, J. F. Thorpe, *J. C. S.* **1906**. 1906.



while benzoyl cyanide forms a triple polymer of a different type again, whose formula is probably[1]:—



as well as a double polymer which seems to have the structure[2]:—



The formation of polymers of the cyanalkine type is obviously impossible in the last two cases, since there is no hydrogen attached to the carbon carrying the CN group.

ISOCYANIDES, ISONITRILES, OR CARBYLAMINES

The isocyanides were first prepared by Gautier in 1866 by the action of silver cyanide on the alkyl iodides. Shortly afterwards Hofmann obtained them by the action of chloroform and alcoholic potash on primary amines:—

$$CH_3{\cdot}NH_2 + CHCl_3 = CH_3{\cdot}N{=}C + 3\,HCl.$$

These two reactions are still the most important for their preparation. They are also got as by-products in the preparation of the nitriles.

They are volatile liquids with a very powerful and extraordinarily repulsive smell. They are not basic, but nevertheless combine with hydrochloric acid in ethereal solution to form compounds such as $2CH_3NC, 3HCl$: these, however, are not stable to water, as aqueous hydrochloric acid readily saponifies the isocyanides to form an amine and formic acid:—

$$Et{\cdot}N{=}C + 2\,H_2O = Et{\cdot}NH_2 + H{\cdot}COOH.$$

This is the most typical reaction of the isocyanides, and proves their constitution. It is to be noticed that whereas the nitriles are saponified with equal ease by acids and alkalies, but only on warming, the isocyanides are stable towards alkali, but are saponified with great readiness—almost explosively in some cases—by acids in the cold.

As the nitriles by taking up one molecule of water are converted into the amides of the corresponding acids, so the isocyanides take up a molecule of water to give the corresponding alkyl-formamides:—

$$Et{\cdot}N{=}C + H_2O = Et{\cdot}NH{\cdot}C\langle{}^{O}_{H}.$$

This change may be brought about by means of glacial acetic acid. The

[1] Diels, Stein, *Ber.* **40.** 1655 (1907). [2] Diels, Pillow, *Ber.* **41.** 1893 (1908).

necessary water is supplied by the acid, which is thereby converted into its anhydride.

On reduction the isocyanides yield secondary amines, one of the groups being of course methyl:—

$$\phi\cdot N{=}C \longrightarrow \phi\cdot NH\cdot CH_3.$$

The hydrolysis of the isocyanides to an amine and formic acid proves that the CN group is linked to the hydrocarbon radical by the nitrogen and not by the carbon. But this grouping may be written in two ways, either as $R\cdot N{\equiv}C$ or as $R\cdot N{=}C$. In the first case the carbon is represented as tetrad, in the second as dyad. The first formula was that originally adopted, but subsequent investigations, especially those of Nef, have shown that the second, with the nitrogen doubly linked to dyad carbon, is much more probable, and in fact practically certain.

To begin with, there are great difficulties in giving a physical interpretation to the first formula. If we hold, as we must, that the carbon atom is of the form of a tetrahedron, we should have to suppose that the nitrogen atom is of such a shape that it is able to surround it entirely, touching all the four points at once, and this does not seem probable; moreover, apart from these compounds, there is no established case in the whole of chemistry of a quadruple bond. Further, the behaviour of the isocyanides strongly supports the dyad carbon structure. A body of the type $R\cdot N{\equiv}C$, in forming an addition-compound, must, like a nitrile, break one of the bonds between the carbon and the nitrogen, so that the product would have the structure $\overset{R\cdot N-C\cdot Y}{\underset{X}{\cdot}}$. A body of the type $R\cdot N{=}C$ might indeed behave in the same way, giving a product $\overset{R\cdot N-C''\cdot Y}{\underset{X}{\cdot}}$; but as the dyad condition for carbon is very abnormal, we should rather expect that the carbon would first assume its normal valency of four by attaching both of the two added groups to itself, forming $R\cdot N{=}C\langle\overset{Y}{X}$: a reaction which could not take place with a derivative of tetravalent carbon, $R\cdot N{\equiv}C$. Thus the difference between the two alternative formulae for the isocyanides is not merely formal, but is real, and conditions a difference in behaviour; and this enables us to decide which is correct. Nef[1] has shown that in the addition-reactions of the isocyanides the primary product possesses, certainly in many cases, and probably in all, the second of the two possible constitutions, having both of the new groups attached to the carbon. For example, the isocyanides reduce mercuric oxide to metallic mercury, being converted into isocyanates:—

$$Et\cdot N{=}C + HgO = Et\cdot N{=}C{=}O + Hg.$$

Again, phenyl isocyanide in chloroform solution adds on two atoms of chlorine to the carbon, forming isocyanphenyl chloride, $\phi\cdot N{=}C\langle\overset{Cl}{Cl}$. In the same way, when the isocyanides are treated with phenyl magnesium bromide, addition takes place to the carbon only, giving a compound $Et\cdot N{=}C\langle\overset{\phi}{Mg\cdot Br}$, the struc-

[1] *Ann.* **270.** 267 (1892); **287.** 265 (1895).

ture of which is proved by its giving with minerals first an imino-compound Et·N=CH·ϕ, and then benzaldehyde. It is thus evident that whereas a nitrile adds on both to the carbon and to the nitrogen, forming compounds of the type $\overset{\dot{X}}{R\cdot C=N\cdot Y}$, an isocyanide does not form the analogous bodies $\overset{\dot{X}}{R\cdot N-C\cdot Y}$, but adds on to the carbon only, giving $R\cdot N=C\langle\overset{X}{Y}$. This can only be explained if the carbon in the isocyanides is dyad, and in the formation of the addition-compounds assumes its higher valency of four.

Constitution of Prussic Acid and its salts

This is a question of great complexity, on which every possible theory has been advanced; and it cannot even now be said that any one of them is established. From the relation between prussic acid and cyanogen, in which it can be proved that the two CN groups are united through carbon, and also from the fact that the nitriles were the first class of organic derivatives to be discovered, it was for a long time assumed that free prussic acid possessed the formula H·C≡N. This view became more firmly established when Gautier, the discoverer of the isocyanides, published in 1869 an elaborate comparison of the reactions of prussic acid with those of the nitriles on the one hand and the isocyanides on the other, from which he concluded that the nitriles were the true analogues of prussic acid. Of recent years this view has been challenged, especially by Nef, who brought forward much evidence in favour of the opposite theory that prussic acid is H·N=C, and its salts M·N=C. Nef's theory has since been attacked by Wade,[1] who thinks that the acid is H·C≡N, while he agrees with Nef that the salts are M·N=C. Others maintain that the alkaline salts are nitriles, M·C≡N, but that the salts of the heavy metals, such as silver and mercury, are isocyanides, M·N=C.

Ostwald points out, in favour of the isocyanide structure for the free acid, that the influence of the true nitrile group, –CN, in raising the acidity of an organic acid is enormous, as is shown by the following series of dissociation constants:—

Acetic acid	K = 0·0018
Monochloracetic	0·155
Monobromacetic	0·138
Cyanacetic	0·370
Thiocyanacetic	0·265

Thus the negative influence of cyanogen is more than twice as great as that of chlorine or bromine; in fact it is among the most strongly acidic groups known. We should therefore expect a compound H·C·N to be among the strongest acids, as is thiocyanic acid, which on chemical grounds we know to be H·S·C≡N. But as a fact prussic acid is among the weakest. It therefore cannot be H·C·N, but must be H·N·C.

To this argument Wade[2] answers that the substitution of the group CCl_3 for

[1] *J. C. S.* **1902.** 1596. [2] l. c. 1615.

hydrogen enormously raises the strength of an acid, as is shown by the comparison of formic with trichloracetic acid :—

Formic acid	K = 0·0214
Trichloracetic	120·0

Hence, if Ostwald's analogy holds, chloroform ought to be an acid of immense strength ; whereas it is not an acid at all. This objection is certainly difficult to answer.

Of the other arguments which have been advanced, some may be dismissed at once: such as the formation of prussic acid (as a nitrile) by heating formamide, since a tautomeric change is obviously probable in a reaction of this kind. The same may be said of Chattaway's argument for the isocyanide formula from the undoubted fact that the cyanogen halides have the halogen attached to nitrogen. The whole question is whether the two classes of bodies are analogously constituted or not.

The problem really divides itself into two parts : the constitution of prussic acid, and that of its salts. The free acid, in the liquid, dissolved, or gaseous state, must, as a tautomeric substance, be a mixture of the two forms ; and hence when we ask what its structure is, we are really asking which of the two predominates. If their proportions are not very unequal, we cannot expect a definite answer. But the salts in the solid state, or at least any given salt, must have one form only ; and even in solution we should expect to find that one form greatly predominated. The facts agree with this. The arguments as to the structure of the metallic cyanides point fairly definitely to the isocyanide formula ; but with regard to the free acid there is very much more doubt. Wade points out that the hydrolysis of a prussic acid resembles that of a nitrile and not that of an isocyanide ; it is effected only slowly by strong acids, which hydrolyse an isocyanide almost explosively, but it is also effected by boiling alkalies, which have no action on an isocyanide. Again, all organic isocyanides dissolve silver cyanide at the ordinary temperature, while nitriles do not. The alkaline cyanides have this power, but not prussic acid, which thus appears as a nitrile. Further, prussic acid forms additive compounds with stannous chloride, antimony pentachloride, and cuprous chloride, herein resembling the nitriles but not the isocyanides. Its reaction with diazomethane has already been referred to. Now that it has been shown that this produces methyl isocyanide as well as methyl cyanide, this reaction cannot be regarded as throwing any light on the question. Nef[1] finds that prussic acid is not acted on by ethyl hypochlorite at − 15°, whereas ethyl isocyanide acts violently at this temperature. Brühl[2] has shown that its molecular refraction is much lower than that required for an isocyanide, and agrees with that of a nitrile. On the other hand Lemoult[3] finds that its heat of combustion is exactly that calculated for H·N·C from the values obtained for isocyanides, and is lower than that required for a nitrile. Its high dielectric constant[4] and its great ionizing power[5] both show an analogy to the nitriles ; but the behaviour of the isocyanides in these respects is unknown.

[1] *Ann.* **287.** 274 (1895). [2] *Z. Ph. Ch.* **16.** 512 (1895).
[3] *C. R.* **143.** 902 (1907) ; **148.** 1602 (*C.* **09.** ii. 272).
[4] Schlundt, *J. Phys. Chem.* **5.** 157 (1901). [5] Centnerszwer, *Z. Ph. Ch.* **39.** 218 (1897).

The physiological effects of prussic acid are stated by Nef to resemble those of an isocyanide; and by Wade, with equal confidence, to be almost identical with those of a nitrile, so that this evidence must be considered to be ambiguous. Great stress has been laid on the smell, but all that can really be said is that while the smell of the nitriles is rather pleasant, those of prussic acid and the isocyanides are very repulsive; they are not very similar. Nef shows that the smell of prussic acid can scarcely be distinguished from that of fulminic acid, which he has proved to be H·O·N=C″. But if the smell of isocyanogen is so powerful as it appears to be, that of prussic acid may be due only to a small proportion of H·N·C, the acid being mainly H·C·N.

It would seem that the balance of evidence is, on the whole, in favour of the nitrile formula for free prussic acid, but it is very unsatisfactory, which is, perhaps, inevitable. When we come to the salts, the ground is rather firmer. Take first those of the alkalies. Nef has shown that most of their reactions can only be explained on the supposition that the primary product is of the type $K{\cdot}N{=}C{<}^{X}_{Y}$. For example, with ethyl hypochlorite potassium cyanide gives ethyl cyanimido-carbonate. This is inexplicable on the nitrile formula, but it can easily be explained on the other theory by the following series of reactions:—

$$\begin{matrix} Et{\cdot}O{\cdot}Cl \\ +\ K{\cdot}N{=}C \end{matrix} = K{\cdot}N{=}C{<}^{OEt}_{Cl} \xrightarrow{C{=}N{\cdot}K} K{\cdot}N{=}C{<}^{OEt}_{Cl{\cdot}C{=}N{\cdot}K} \xrightarrow{H_2O} H{\cdot}N{=}C{<}^{OEt}_{C-N} + KOH + KCl.$$

So, too, it is probable that potassium cyanide combines with chlorine to give $K{\cdot}N{=}C{<}^{Cl}_{Cl}$, as it certainly does with oxygen to form K·N=C=O; and there are many other cases.

Again, the alkaline cyanides form stable double salts with many salts of the heavy metals. The isocyanides do the same, while the corresponding compounds of the nitriles, where they exist at all, are much less stable.[1]

The cyanides of the heavy metals, and especially those of silver and mercury, have in many respects a different behaviour from the alkaline salts. For example, they cannot be oxidized by potassium permanganate, as those of the alkalies can; and on treatment with alkyl halides they yield mainly isocyanides, whereas the alkaline salts give mainly nitriles. This last reaction will be discussed later; but the other differences, though they may be due to a difference in structure between the two classes of salts, are, in all probability, sufficiently accounted for by the fact that the cyanides of the heavy metals are scarcely ionized at all, and hence their reactions are those of the undissociated compound, while those of the alkaline salts are those of their ions. We may therefore conclude that the metallic cyanides all have the metal attached to the nitrogen.

We have still to consider the reaction of the metallic cyanides with alkyl and acyl halides.[2] The alkaline cyanides with the alkyl halides give mainly nitriles,

[1] Hofmann, Bugge, *Ber.* **40.** 1772; Ramberg, ib. 2578 (1907).

[2] Cf. Guillemard, *C. R.* **143.** 1158; **144.** 141, 326 (1907); *Ann. Chim. Phys.* [8] **14.** 311 (*C.* **08.** ii. 583).

but especially in the presence of solvent small quantities (up to 5 per cent.) of isocyanides are formed. Alkyl sulphuric or sulphonic acids, or alkyl sulphates, produce the same result.[1] Silver cyanide, and the other heavy metal cyanides, so far as they have been investigated, give with alkyl halides practically only isocyanides[2]; but with acyl halides, such as acetyl and benzoyl chlorides (and also apparently with certain substituted alkyl halides, as the chloro-methyl ether $Cl{\cdot}CH_2{\cdot}OAlk$[3]), they form nitriles.

Gautier supposed that the salts were all M·C·N, and that a nitrile was always the primary product, but that this changed over into an isocyanide (where that was the ultimate product) in the course of the reaction. This view has been shown to be untenable, as the change does not occur; and so has a later view, that the primary product is always an isocyanide, which in some cases changes over into a nitrile: because, although this change does occur, it only does so very slowly under the conditions of the experiment.

Again, it has been suggested that the potassium salt is K·C·N, and the silver salt Ag·N·C. But against this we have all the evidence that the potassium salt is K·N·C, and, moreover, it leaves us with the same difficulty of explaining how Ag·N·C with acyl chlorides gives nitriles.

Nef, regarding all the salts as of the type M·N·C, considers that the isocyanides are produced from silver cyanide by direct replacement:—

$$Ag{\cdot}N{=}C + Alk{\cdot}I = Alk{\cdot}N{=}C + AgI,$$

and that where nitriles are produced, this is due to the intermediate formation of addition-compounds:—

$$K{\cdot}N{=}C + Alk{\cdot}I = K{\cdot}N{=}C\begin{matrix}\nearrow Alk\\ \searrow I\end{matrix} = KI + N{=}C{\cdot}Alk.$$

It can be shown that the metallic cyanides do in many cases combine with the halides; we know that dyad carbon forms additive compounds of this type; and in similar cases Nef has actually prepared additive compounds containing both metal and halogen. Thus his theory seems satisfactory as far as the formation of nitriles is concerned. But there is evidence that additive compounds are formed also in the cases where an isocyanide is the ultimate product. Dry silver cyanide absorbs methyl iodide at its boiling-point, giving a viscous liquid which solidifies on cooling, and evolves methyl isocyanide on further heating. What structure is to be attributed to these compounds? Wade, who accepts Nef's view as to the formation of nitriles, suggests that the intermediate compounds produced in those cases in which an isocyanide is obtained have the alkyl and the halogen attached to the nitrogen thus:—

$$Ag{\cdot}N{=}C + CH_3{\cdot}I = Ag{\cdot}\overset{\displaystyle I}{\underset{\displaystyle CH_3}{\dot{N}}}{=}C = \begin{matrix}AgI & +\\ CH_3{\cdot}N{=}C.\end{matrix}$$

The objection to this view is that there is no evidence for the structure of these additive compounds, beyond the fact that their supposed analogues, the com-

[1] Auger, *C. R.* **145**. 1287 (1908).

[2] The nitrile is, however, formed in increasing quantity as the alkyl group gets larger.

[3] Sommelet, *C. R.* **143**. 827 (1907).

pounds of the alkyl halides with the isocyanic esters, yield on hydrolysis very small quantities of secondary amines; and this is not a proof of the structure of these compounds, much less of those obtained from the metallic cyanides. Moreover, the structure assigned to them is intrinsically improbable; for we must suppose that the halogen attaches itself to the nitrogen, for which it has very little affinity, rather than to the excessively active dyad carbon atom.

It seems more natural to suppose that in both cases—whether the final product is a nitrile or an isocyanide—the addition takes place to the dyad carbon. And it is not difficult to see how this might lead to the formation of an ester of either type.[1] On this hypothesis, the body formed by the addition of any metallic cyanide to any alkyl or acyl halide will have the structure $M{\cdot}N{=}C\begin{matrix}\diagup\mathrm{Alk}\\ \diagdown\mathrm{I}\end{matrix}$, or, as it may also be written, $\begin{matrix}\mathrm{Alk{\cdot}C{\cdot}I}\\ \|\\ \mathrm{M{\cdot}N}\end{matrix}$. This latter formulation shows that there is a formal analogy between the structure of the compound and that of the unsymmetrical oximes. It has a carbon atom linked to two different groups, and doubly linked to trivalent nitrogen. It obviously can occur in two stereoisomeric forms:—

$$\begin{matrix}\mathrm{Alk{\cdot}C{\cdot}I}\\ \|\\ \mathrm{M{\cdot}N}\end{matrix} \quad \text{and} \quad \begin{matrix}\mathrm{Alk{\cdot}C{\cdot}I}\\ \|\\ \mathrm{N{\cdot}M}\end{matrix}$$

In the second of these, which may be called the synhaloid form, the metal and the iodine, being near to one another, will split off easily as metallic iodide, leaving a nitrile, just as a synaldoxime loses water:—

$$\begin{matrix}\mathrm{Alk{\cdot}C{\cdot}I}\\ \|\\ \mathrm{N{\cdot}M}\end{matrix} = \begin{matrix}\mathrm{Alk{\cdot}C}\\ \|\|\\ \mathrm{N}\end{matrix} + \mathrm{MI} \quad : \quad \begin{matrix}\mathrm{Alk{\cdot}C{\cdot}H}\\ \|\\ \mathrm{N{\cdot}OH}\end{matrix} = \begin{matrix}\mathrm{Alk{\cdot}C}\\ \|\|\\ \mathrm{N}\end{matrix} + \mathrm{H_2O}.$$

This is essentially Nef's formulation of the reaction of potassium cyanide, the formation of nitriles. On the other hand the anti-compound cannot react in this way, because the metal and the halogen are on opposite sides of the C≡N group. It therefore undergoes the Beckmann reaction, which brings the metal and the halogen nearer together, so that they can split off, giving an isocyanide:—

$$\begin{matrix}\mathrm{Alk{\cdot}C{\cdot}I}\\ \|\\ \mathrm{M{\cdot}N}\end{matrix} \rightarrow \begin{matrix}\mathrm{M{\cdot}C{\cdot}I}\\ \|\\ \mathrm{Alk{\cdot}N}\end{matrix} \rightarrow \begin{matrix}\mathrm{C}\\ \|\\ \mathrm{Alk{\cdot}N}\end{matrix} + \mathrm{MI}.$$

This is analogous to the formation of an isocyanate from the potassium salt of an amide in the Hofmann reaction:—

$$\begin{matrix}\mathrm{Alk{\cdot}C{\cdot}OK}\\ \|\\ \mathrm{Br{\cdot}N}\end{matrix} \rightarrow \begin{matrix}\mathrm{Br{\cdot}C{\cdot}OK}\\ \|\\ \mathrm{Alk{\cdot}N}\end{matrix} \rightarrow \begin{matrix}\mathrm{C{=}O}\\ \|\\ \mathrm{Alk{\cdot}N}\end{matrix} + \mathrm{KBr}.$$

On this hypothesis everything depends on which stereoisomer is produced; the synhaloid gives a nitrile, and the antihaloid an isocyanide. We must therefore suppose that with an alkyl iodide and potassium cyanide, or with an alkyl acyl halide and silver cyanide, the synhaloid form is obtained; while the antihaloid is formed from an alkyl halide and silver cyanide:—

$$\begin{matrix}\mathrm{Alk{\cdot}C{\cdot}I}\\ \|\\ \mathrm{N{\cdot}K}\end{matrix} \quad : \quad \begin{matrix}\mathrm{Ac{\cdot}C{\cdot}Cl}\\ \|\\ \mathrm{N{\cdot}Ag}\end{matrix} \quad : \quad \begin{matrix}\mathrm{Alk{\cdot}C{\cdot}I}\\ \|\\ \mathrm{Ag{\cdot}N}\end{matrix}$$

[1] Sidgwick, *Proc. C. S.* **21**. 120 (1905).

CYANIC ACID

Cyanic acid, HCNO, like hydrocyanic acid, gives two series of derivatives; and it may therefore have either or both of the formulae H·O·C≡N and H·N=C=O. It is by no means certain which of these should be adopted, but the imide formula, M·N=C=O, is at any rate the more probable as far as the salts are concerned. This is most nearly related to the formula of the metallic cyanides, M·N=C″, and it explains the ease with which the latter are converted into cyanates, the dyad carbon atom taking up an atom of oxygen to become tetrad.

Cyanic acid is prepared from its polymer cyanuric acid $C_3N_3O_3H_3$, which is obtained by the action of water on cyanuric bromide, $C_3N_3Br_3$, or by heating urea[1]:—

$$3\ CO(NH_2)_2 = C_3N_3O_3H_3 + 3\ NH_3.$$

The cyanuric acid is heated in a stream of carbon dioxide, and the vapours of cyanic acid which are evolved are condensed to a liquid in a freezing mixture. Cyanic acid is a very volatile liquid, giving an acrid and corrosive vapour. It is excessively unstable. In about an hour, if it is kept below 0°, it is completely converted into a white porcelain-like mass: this is generally said to consist of cyamelide, an insoluble polymer of cyanic acid which regenerates cyanic acid on heating. It has been shown,[2] however, that this mass is composed of about 30 per cent. cyamelide and 70 per cent. cyanuric acid. If the liquid cyanic acid is taken out of the freezing mixture it changes into this white mass with explosive violence in the course of a few minutes. (Formaldehyde undergoes a similar explosive polymerization to the triple polymer trioxymethylene.[3]) If it is dissolved in ether, or if a few drops of triethyl-phosphine, PEt_3, are added to it, it is converted into cyanuric acid.

In aqueous solution it is scarcely more stable, and rapidly breaks up, at any temperature above 0°, into carbonic acid and ammonia. The potassium salt breaks up in the same way in solution, but is quite stable in presence of a slight excess of potash.[4]

Potassium cyanate is obtained by heating potassium cyanide or ferrocyanide with an oxidizing agent such as manganese dioxide, litharge, or potassium bichromate; or by the electrolytic oxidation of potassium cyanide in aqueous solution.[5] It is of course on its ready oxidation to the cyanate that the use of potassium cyanide as a reducing agent in inorganic chemistry depends. The cyanate is also got by passing cyanogen gas or cyanogen chloride into potash solution, in the first case together with potassium cyanide, in the second with potassium chloride.

It is to be noticed that silver cyanate, unlike the cyanide, reacts with acyl chlorides to give acyl isocyanates, and not the normal esters.[6] Also, free cyanic acid with diazomethane gives only methyl isocyanate.[7]

[1] Cf. v. Walther, *J. pr. Ch.* [2] **79.** 126 (*C.* **09.** i. 841).
[2] Senier, Walsh, *J. C. S.* **1902.** 290.
[3] Kekulé, *Ber.* **25.** 2435 (1892).
[4] Siepermann, *C.* **07.** i. 1559.
[5] Paterno, *C.* **04.** ii. 982.
[6] Billeter, *Ber.* **38.** 3213 (1903); **38.** 2013, 2015 (1905).
[7] Palazzo, Carapelle, *C.* **06.** ii. 1723.

Cyanic acid gives rise to the following series of derivatives:—

1. The halides of cyanogen, or acid halides of cyanic acid, such as CN·Cl.

2. The amide, cyanamide, $C\begin{smallmatrix}NH_2\\ \diagdown\!\!\diagup\\ N\end{smallmatrix}$ (or carbo-diimide, HN=C=NH), and its derivatives.

3. The cyanic and isocyanic esters.

4. The thiocyanic and isothiocyanic esters.

All these classes of compounds can form triple polymers, which will be considered later.

Cyanogen Halides

These bodies are obtained by the action of the halogens on metallic cyanides or on aqueous hydrocyanic acid. On the large scale cyanogen bromide is generally made by the action of sulphuric acid on a mixture of the bromide, bromate, and cyanide of sodium. The velocity of the change has been investigated by Ewan,[1] who stops the reaction at a given point by adding soda, and determines the amount of unchanged sodium cyanide by titration with silver nitrate and potassium iodide. His results indicate that the reaction on which the change depends is:—

$$HBrO_3 + 5\,HBr + 3\,HCN = 3\,BrCN + 3\,HBr + 3\,H_2O.$$

Cyanogen chloride is a colourless, very poisonous liquid, boiling at $+15{\cdot}5°$ and melting at $-6°$. It is somewhat soluble in water. On keeping it changes into cyanuric chloride $C_3N_3Cl_3$. Its formula was originally assumed to be that of a normal cyanogen derivative, N≡C·Cl. But Chattaway[2] has shown that this is not the case. When a halogen atom is attached to carbon, it yields fairly stable compounds; or if the negative character of the body loosens the bond between the two (as in the acid chlorides), then on treatment with water the chlorine is removed as hydrochloric acid, and hydroxyl takes its place:—

$$X{\cdot}C{\cdot}Cl + HOH = X{\cdot}C{\cdot}OH + HCl.$$

Where the halogen is joined to triad nitrogen, as in the halogen-substituted amines and amides, Chattaway finds that it behaves quite differently. It can easily be removed, but is replaced not by hydroxyl but by hydrogen, the chlorine forming hypochlorous instead of hydrochloric acid. The typical reactions of chlorine attached to trivalent nitrogen are thus reactions of hypochlorous acid, that is, oxidations. Such bodies oxidize sulphurous acid to sulphuric, hydriodic acid to iodine, and hydrogen sulphide to sulphur. All these reactions are given quantitatively by the cyanogen halides:—

$$C{=}N{\cdot}Br + 2\,HI = HCN + HBr + I_2,$$
$$C{=}N{\cdot}Br + H_2SO_3 + H_2O = HCN + HBr + H_2SO_4,$$
$$C{=}N{\cdot}Br + H_2S = HCN + HBr + S.$$

This is strong evidence that these halides are really isocyanogen compounds. It also supports Nef's view that the isocyanides contain divalent carbon. For these characteristic reactions are those of chlorine attached to triad nitrogen. If the nitrogen is pentad, the chlorine behaves quite differently, as we see in

[1] *J. Soc. Chem. Ind.* **25**. 1130 (*C.* **07**. i. 591).
[2] Chattaway, Wadmore, *J. C. S.* **1902**. 191.

ammonium chloride. The structure C≡N·Cl is therefore excluded, and we must fall back on the dyad carbon.

When cyanogen chloride is treated with ammonia, it gives cyanamide, $H_2N{\cdot}C{\equiv}N$. This was regarded as a proof of the normal formula, from which it follows by direct substitution. But it can easily be derived from the isocyanogen formula by Nef's addition method:—

$$NH_3 + C{=}N{\cdot}Cl = \begin{matrix} H_2N \\ H \end{matrix}\!\!>\!C{=}N{\cdot}Cl = H_2N{\cdot}C{\equiv}N + HCl.$$

Cyanogen iodide gives a curious reaction when its ethereal solution is treated with zinc. It yields zinc cyanide, with separation of iodine. Regarding the zinc salt as an isocyanide, this is a case of direct substitution:—

$$\begin{matrix} C{=}N{\cdot}I \\ C{=}N{\cdot}I \end{matrix} + Zn = \begin{matrix} C{=}N \\ C{=}N \end{matrix}\!\!>\!Zn + I_2.$$

The cyanogen halides, and especially the bromide, have been the subject of numerous investigations. Some of the more important of their reactions are described in the papers referred to below.[1]

Cyanamide

Cyanamide, $C\!\begin{matrix} \diagup NH_2 \\ \diagdown\!\diagdown N \end{matrix}$, or possibly, though less probably, HN=C=NH, is best prepared by the action of freshly precipitated mercuric oxide on thio-urea, in the presence of a little ammonium thiocyanate, which dissolves some of the mercuric oxide as the double thiocyanate, and so renders it more active:—

$$S{=}C\!\begin{matrix} \diagup NH_2 \\ \diagdown NH_2 \end{matrix} = C\!\begin{matrix} \diagup NH_2 \\ \diagdown\!\diagdown N \end{matrix} + H_2S.$$

It may also be obtained in many other ways, as by the action of ammonia on cyanogen chloride, or by passing carbon dioxide over heated sodamide:—

$$2\,NaNH_2 + CO_2 = NH_2CN + 2\,NaOH.$$

The cyanamide derivatives have recently assumed a considerable practical importance as affording a method for obtaining atmospheric nitrogen in a combined form for agricultural purposes.[2] In 1904 Caro and Frank showed that when calcium carbide[3] is heated with nitrogen in the electric furnace, carbon separates and calcium cyanamide is formed:—

$$CaC_2 + N_2 = CaN{\cdot}CN + C.$$

The crude product, which contains about 20 per cent. of nitrogen, is known as Kalkstickstoff, and is used as a manure. It is hydrolysed in the soil to form cyanamide, urea, and ammonia. It has to be used with care, as some of the earlier products of hydrolysis, probably the cyanamide, have a poisonous action;

With cyclic amines: v. Braun, *Ber.* **33.** 1483 (1900); **40.** 3914 (1907); with tertiary amines: v. Braun, *Ber.* **36.** 1196 (1903); **40.** 3933 (1907); with hydrazine: Pellizari, Cantoni, *Gaz.* **35.** i. 291 (*C.* **05.** ii. 122); Pellizari, Roncagliolo, ib. **37.** i. 434 (*C.* **07.** ii. 585); Pellizari, ib. **37.** i. 611 (*C.* **07.** ii. 801); with hydroxylamine: Wieland, *Ber.* **38.** 1445 (1905).

[2] Kühling, *Ber.* **40.** 310 (1907); P. F. Frankland, *J. Soc. Chem. Ind.* **26.** 175 (1907).

[3] Barium carbide can also be used. Kühling, Berkold, *Z. angew. Ch.* **22.** 193 (*C.* **09.** i. 629).

but this danger can be avoided by putting on the manure some time before the crop is sown.[1]

Cyanamide forms a colourless deliquescent crystalline mass, melting at 40°, and is easily soluble in water, alcohol, and ether. Its hydrogen atoms are readily replaced by metals. If treated with an ammoniacal silver solution, it gives a yellow precipitate of silver cyanamide, CN_2Ag_2, which on treatment with ethyl iodide forms an ester whose formula is $N{\equiv}C{\cdot}NEt_2$. Like all cyanogen derivatives, cyanamide readily forms addition-compounds. It polymerizes spontaneously to the so-called dicyandiamide,[2] which is probably cyanguanidine, $C(=N{\cdot}CN)(NH_2)_2$. When treated in ethereal solution with hydrochloric acid it gives a compound $CN_2H_2{\cdot}2HCl$. It also undergoes the typical cyanide reactions. It takes up water to form the amide, urea, it forms with hydrogen sulphide the thioamide, thio-urea, and with ammonia the amidine, guanidine:—

$$N{\equiv}C{\cdot}NH_2 + NH_3 = HN{=}C(NH_2)_2.$$

The mono-alkyl cyanamides are obtained from cyanogen chloride and primary amines:—

$$\phi{\cdot}NH_2 + Cl{\cdot}CN = \phi{\cdot}NH{\cdot}CN \text{ or } \phi{\cdot}N{=}C{=}NH:$$

or by the action of mercuric oxide on the mono-alkyl thio-ureas:—

$$S{=}C(NH{\cdot}CH_3)(NH_2) - H_2S = C(NH{\cdot}CH_3){\equiv}N \text{ or } C(N{\cdot}CH_3){\equiv}NH.$$

There is the same doubt about their formulae as about that of cyanamide itself.

Among the di-substitution products, on the other hand, the derivatives of both forms are known. The true cyanamide derivatives, $N{\equiv}C{\cdot}NR_2$, are formed, as has been mentioned, from silver cyanamide and alkyl iodide, and their constitution is shown by the fact that on decomposition they yield dialkylamines. They are also formed from the dialkyl chloramines and potassium cyanide:—

$$Et_2N{\cdot}Cl + KNC = KCl + Et_2N{\cdot}C{\equiv}N,$$

which is a further proof of their structure.

The derivatives of the other form have already been discussed as carbodiimide compounds. They are formed by the action of mercuric oxide on certain symmetrical di-substituted thio-ureas:—

$$S{=}C(NH{\cdot}C_3H_7)(NH{\cdot}C_3H_7) = C(N{\cdot}C_3H_7){\equiv}(N{\cdot}C_3H_7) + H_2S.$$

Esters of Cyanic Acid

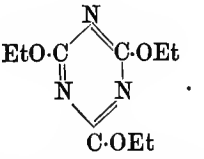
The normal esters of cyanic acid,[3] $R{\cdot}O{\cdot}C{\equiv}N$, are said to have been obtained by the action of cyanogen chloride on sodium ethylate. But later work has shown that this is a mistake, and as a fact they have not yet been isolated by

[1] Pollacci, *Z. Elektrochem.* **14.** 565; Ulpiani, *Gaz.* **38.** ii. 358 (*C.* **08.** ii. 1342, 1627); Löhnis, Moll, *C.* **09.** i. 310; Kappen, ib.; Loew, ib. 785.

[2] Cf. Pohl, *J. pr. Ch.* [2] **77.** 533 (*C.* **08.** ii. 151).

[3] Cf. Nef, *Ann.* **287.** 310 (1895).

any means whatever. It is, however, clear that they must be the primary product of this reaction, since the substance actually obtained is the normal cyanuric ester:—



It would seem, therefore, that the normal cyanic esters have in such a high degree the tendency to polymerization which characterizes the whole group, that they condense to cyanurates as soon as they are formed.

On the other hand, the isocyanic esters, R·N=C=O, are well known. They were first prepared by Wurtz in 1854 by distilling the salts of the alkyl sulphuric acids with potassium cyanate, and led him to the discovery of the amines. A better method is to act with alkyl iodide on silver cyanate.

They are also got by oxidizing the isocyanides with mercuric oxide; and by the action of bromine on amides, being intermediate products in the Hofmann reaction for preparing amines. They may be obtained by the action of carbonyl chloride on amines. If carbonyl chloride is passed over the heated amine hydrochloride, a carbamic chloride is formed, which on treatment with lime loses hydrochloric acid to give an isocyanate:—

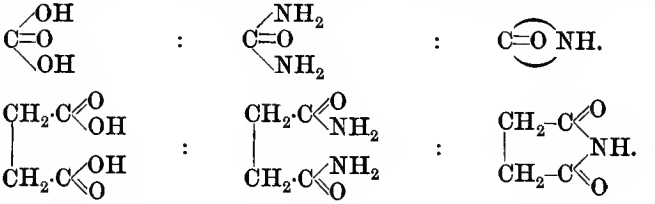
$$\begin{aligned} Cl{\cdot}CO{\cdot}Cl + H_2N{\cdot}Et &= Cl{\cdot}CO{\cdot}NH{\cdot}Et + HCl \\ &= O{=}C{=}N{\cdot}Et + 2\,HCl. \end{aligned}$$

Another method of making them is by a modification of the Hofmann mustard oil reaction, using carbon oxysulphide instead of carbon bisulphide.[1] This reacts with a primary amine to give a thiocarbamic acid, which, on treatment with mercuric oxide, loses hydrogen sulphide and yields the isocyanate:—

$$COS + Et{\cdot}NH_2 = \begin{matrix} SH \\ C{=}O \\ NH{\cdot}Et \end{matrix} = H_2S + O{=}C{=}NEt.$$

The isocyanic esters are volatile liquids of a powerful, unpleasant smell, which, on keeping, change rather rapidly into the polymeric isocyanuric esters.

They are, of course, derivatives of the imide of carbonic acid; compare:—



Dibasic Acid. Diamide. Imide.

The great strain in the molecule causes them to react readily with the breaking of a double link. Now there are in the molecule two double links, one between the carbon and the nitrogen, and the other between the carbon and the oxygen. Of these two the latter is comparatively stable. The carbonyl compounds—

[1] Anschütz, *Ann.* 359. 202 (1908).

aldehydes, ketones, acids—though they can behave as unsaturated bodies, are yet capable in a great number of reactions of maintaining the carbonyl group intact. On the other hand the imide group, $>C{=}NH$, is an extremely unstable one. Accordingly we find that in the reactions of the isocyanates it is always the imide group that is attacked, and in consequence these reactions are very similar to those of the isocyanides, in which the double link between the carbon and the nitrogen is almost always broken, while the carbon becomes tetrad; and in this case also it is nearly always a hydrogen atom which goes to the nitrogen, while the residue of the added molecule attaches itself to the carbon.

The most important reaction of the isocyanates is one in which the carbon and nitrogen are completely separated. If they are warmed with alkali they split up into carbon dioxide and an amine, which proves their constitution:—

$$\begin{matrix} CH_3{\cdot}N{=}C{=}O \\ + \quad H_2O \end{matrix} \quad = \quad CH_3{\cdot}NH_2 \; + \; O{=}C{=}O.$$

But often this link is not completely broken; for example, with alcohols they give urethanes:—

$$O{=}C{=}N{\cdot}CH_3 \; + \; C_2H_5{\cdot}OH \quad = \quad O{=}C\begin{matrix}NH{\cdot}CH_3 \\ OC_2H_5\end{matrix}.$$

With ammonia or primary or secondary amines they give substituted ureas:—

$$O{=}C{=}N{\cdot}CH_3 \; + \; H{\cdot}NH{\cdot}C_2H_5 \quad = \quad O{=}C\begin{matrix}NH{\cdot}CH_3 \\ NH{\cdot}C_2H_5\end{matrix}.$$

By a combination of the first and last of these reactions, they give, when boiled with water alone, symmetrical di-substituted ureas. One molecule breaks up into carbon dioxide and an amine, and then the latter reacts with a second molecule of isocyanate to form the urea. They combine directly with hydrochloric acid to form substituted carbamic chlorides:—

$$O{=}C{=}N{\cdot}CH_3 \; + \; HCl \quad = \quad O{=}C\begin{matrix}NH{\cdot}CH_3 \\ Cl\end{matrix}.$$

This reaction is to be contrasted with that of an isocyanide with hydrochloric acid, which is due to the dyad carbon:—

$$R{\cdot}N{=}C \; + \; HCl \quad = \quad R{\cdot}N{=}C\begin{matrix}H \\ Cl\end{matrix}.$$

Phenyl isocyanate, $\phi{\cdot}N{=}C{=}O$, is a substance which has been much used for determining questions of constitution. Although it may be obtained by any of the ordinary reactions for preparing isocyanates, and also by one of the Sandmeyer reactions, by treating diazobenzene with potassium cyanate and copper powder, it is unfortunately difficult to prepare in any quantity, as the yield by any of these methods is small.

The use of phenyl isocyanate as a reagent for determining constitution is due to Goldschmidt,[1] who first applied it in the case of succinosuccinic ester and analogous compounds, and shortly afterwards to the more important case of the oximes. It enables us to detect the presence of hydroxyl and imide or amide groups, as with hydroxyl it gives urethanes:—

$$X{\cdot}C{\cdot}OH \; + \; C\begin{matrix}N\phi \\ O\end{matrix} \quad = \quad \begin{matrix}NH{\cdot}\phi \\ C{=}O \\ O{\cdot}C{\cdot}X\end{matrix},$$

[1] *Ber.* **23.** 2179 (1890); Dieckmann, *Ber.* **33.** 2002 (1900).

while with amines or imines it gives urea derivatives:—

$$X\cdot C{=}NH + C\begin{cases} N\phi \\ O \end{cases} = C\begin{cases} NH\cdot\phi \\ =O \\ N{=}C\cdot X \end{cases}.$$

It is especially useful from the fact that it can be made to react at a low temperature and in the absence of a solvent. There is thus less danger that the reagent itself will bring about tautomeric change, which is particularly liable to happen where a solvent of some ionizing power, such as alcohol, has to be used. Also it breaks up the substance with which it reacts, and adds on the two parts to itself in such a way that they can be easily identified.

The cases where it has proved most useful are those of the oximes, and of bodies with keto-enolic tautomerism. In the oximes the question was whether the two isomeric benzaldoximes had the formulae $\begin{matrix}\phi\cdot C\cdot H \\ \| \\ N\cdot OH\end{matrix}$ and $\phi\cdot CH\begin{matrix}\cdot NH \\ \diagdown \\ \diagup O\end{matrix}$ (of which the first would give a urethane and the second a urea), or whether they both had the first formula; and Goldschmidt showed that in both cases a urethane was formed.

In the case of the keto-enolic esters, such as the β-keto-esters, the problem is a different one. We have here to decide between the groupings $-CH{=}C\cdot OH$ and $-CH_2-C{=}O$. The former gives a urethane, while the latter does not react at all. It has, however, recently been shown[1] that this test must be used with caution, as some ketonic compounds are able to react with phenyl isocyanate, changing over into their isomers in the course of the reaction. But Goldschmidt[2] finds that this danger is to a great extent avoided if care is taken to exclude traces of alkali, which have a great power of promoting the tautomeric change, and will often enable the isocyanate to react with the ketonic form when it cannot do so in their absence.[3] Even then, however, this reagent is not always trustworthy. There are cases of hydroxyl compounds (especially those with negative substituents) with which it will not react; while there are also cases of undoubted ketones with which it combines by direct addition.[4]

Thiocyanic Acid and its Derivatives

The salts of thiocyanic acid are obtained from the cyanides by direct combination with sulphur, just as those of cyanic acid are got by direct combination with oxygen. But whereas it has been shown that the metallic cyanates have the formula $M\cdot N{=}C{=}O$, that is, are really isocyanates, free thiocyanic acid and its salts are derived from the normal formula $H\cdot S\cdot C{\equiv}N$, $M\cdot S\cdot C{\equiv}N$. Isothiocyanic acid, $H\cdot N{=}C{=}S$, and its salts are unknown. This is in accordance with the general tendency of the $C{=}S$ group to pass into $C\cdot S\cdot H$, which is far greater than that of $C{=}O$ to go over into $C\cdot OH$, as we have already had occasion to notice in comparing the amides with the thioamides and the ureas with the thio-ureas.

Free thiocyanic acid is generally described as a liquid. But this is because it has never until recently been obtained in the pure state. The pure acid[5] can

[1] Michael, *Ber.* **38.** 22 (1905). [2] *Ber.* **38.** 1096 (1905).
[3] Cf. Dieckmann, Hoppe, Stein, *Ber.* **37.** 4627 (1904).
[4] Michael, Cobb, *Ann.* **363.** 64 (1908). [5] Rosenheim, Levy, *Ber.* **40.** 2166 (1907).

be prepared by treating a mixture of dry potassium thiocyanate and phosphorus pentoxide with sulphuric acid in an atmosphere of hydrogen, avoiding any rise of temperature and collecting the vapours evolved in a freezing mixture. It is then found to be a white crystalline mass, which is stable at 0°, but at +5° melts to a liquid which soon begins to polymerize, first turning yellow and then suddenly resolidifying to a yellow amorphous mass. The molecular weight was shown by the boiling-point in ethereal solution to be that required by the formula HCNS. The dilute aqueous solution is stable at 0°, but on warming polymers separate out. The concentrated solution breaks up into hydrocyanic acid and persulphocyanic acid, $H_2C_2N_2S_3$. If a fairly concentrated solution is treated with a large excess of sulphuric acid, it decomposes mainly into ammonia and carbon oxysulphide, COS. When treated with diazomethane at −5°, thiocyanic acid is wholly converted into methyl thiocyanate, CH_3–S–C≡N.[1]

Ammonium thiocyanate may be obtained by the action of carbon bisulphide on alcoholic ammonia:—

$$CS_2 + 4\,NH_3 = C{=}S{<}^{NH_2}_{S\cdot NH_4} + 2\,NH_3 = C{\leqslant}^{N}_{S\cdot NH_4} + (NH_4)_2S.$$

On heating to 160° it gives thio-urea, but if heated for twenty hours to 180° it is converted into guanidine thiocyanate, as we have already seen.

The behaviour of potassium thiocyanate with organic halides[2] is remarkable. With alkyl halides and many of their derivatives, such as chloracetic ester, it gives normal thiocyanic esters, R·S·C≡N. But with bodies of the type Ar_2·CHBr, where Ar is an aromatic radical—for example, with $CH\phi_2Br$—it gives isothiocyanates, R·N=C=S. No explanation has been offered of this.

The brilliant red colour which is produced with ferric salts on addition of potassium thiocyanate solution is due to the formation of a double thiocyanate, 9 KCNS·$Fe(CNS)_3$. It may be distinguished from all other substances which could possibly be mistaken for it by the fact that on shaking with ether it goes over entirely into the ethereal solution. This test is very delicate. A thousandth of a milligram of ferric iron produces a quite visible pink colour.

The esters of thiocyanic acid belong to two series: (1) the normal thiocyanates R·S·C≡N, and (2) the isothiocyanates or mustard oils R·N=C=S.

The normal esters (S-esters) are obtained by the action of potassium thiocyanate on alkyl iodides or the salts of alkyl sulphuric acids, or from cyanogen chloride and the mercaptides, which shows that the alkyl is attached to sulphur:—

$$(EtS)_2Pb + 2\,C{\leqslant}^{Cl}_{N} = 2\,C{\leqslant}^{S\cdot Et}_{N} + PbCl_2.$$

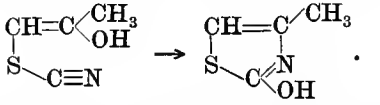
They are liquids of a leek-like smell. Their structure is also shown by their being reduced by nascent hydrogen to mercaptan and prussic acid, which is then further reduced to methylamine. Another proof is that when oxidized with nitric acid they give alkyl sulphonic acids. With alcoholic potash they form potassium thiocyanate, which the isomeric isothiocyanates do not. They have

[1] Palazzo, Scelsi, *Gaz.* **38**. i. 659 (*C.* **08**. ii. 774).

[2] Wheeler, *C.* **02**. i. 1400, ii. 577, 788. Cf. Johnson, Guest, *Am. Ch. J.* **41**. 337 (*C.* **09**. i. 1547), who failed to observe any regularities.

a remarkable tendency to change over into the mustard oils. Methyl thiocyanate is very largely converted into the iso-compound by heating to 180° for several hours, and with allyl thiocyanate the change takes place so easily that if it is once distilled the conversion is complete.

Compounds containing the thiocyanate group in the α-position to carbonyl or carboxyl are capable of intramolecular condensation to heterocyclic bodies. Thus thiocyanacetone (from chloracetone) if heated with sodium carbonate forms methyl-oxy-thiazol :—



The isothiocyanic esters or mustard oils may be obtained from the primary amines, by first combining them with carbon bisulphide to dithiocarbamates :—

$$CS_2 + 2\,H_2N{\cdot}Et = S{=}C\begin{matrix}NH{\cdot}Et\\ S{\cdot}NH_3Et\end{matrix}.$$

This is converted by silver nitrate into the silver dithiocarbamate, which on boiling with water breaks up into silver sulphide, hydrogen sulphide, and the mustard oil :—

$$2\,S{=}C\begin{matrix}NHEt\\ S{\cdot}Ag\end{matrix} = 2\,C\begin{matrix}NEt\\ S\end{matrix} + Ag_2S + H_2S.$$

This is Hofmann's mustard oil test for primary amines, the product being recognized by its smell.

They are also formed by heating the normal thiocyanates, and from the isocyanates by heating them with phosphorus pentasulphide.

The aromatic mustard oils are also got from the condensation product of the primary aromatic amines with carbon bisulphide. This is of course not a dithiocarbamate but a thio-urea, and to convert it into the mustard oil merely requires boiling with concentrated hydrochloric acid :—

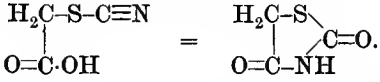
$$S{=}C\begin{matrix}NH\phi\\ NH\phi\end{matrix} + HCl = C\begin{matrix}N\phi\\ S\end{matrix} + \phi{\cdot}NH_3Cl.$$

The mustard oils are liquids of an unpleasant odour, which are insoluble in water and boil undecomposed. Their reactions are almost all strictly analogous to those of the isocyanates. Thus with dilute acid they are hydrolysed to the amine, carbon dioxide, and hydrogen sulphide; with concentrated sulphuric acid they give amine and carbon oxysulphide. They have a large number of additive reactions: for example, they combine with ammonia and amines to form thio-ureas, with alcohols to form thio-urethanes, &c.

Nascent hydrogen converts them into amine and thioformaldehyde, which appears in the form of its trimolecular polymer :—

$$Et{\cdot}N{=}C{=}S + 2\,H_2 = Et{\cdot}NH_2 + H{\cdot}C\begin{matrix}S\\ H\end{matrix}.$$

Isothiocyan-acetic acid,[1] like its normal isomer, goes over readily or even spontaneously into a ring compound, dioxy-thiazol :—



[1] Frerichs, Beckurts, *C.* **00.** i. 589, **02.** ii. 931; Hantzsch, Vögelen, *Ber.* **35.** 1007 (1902).

Allyl isothiocyanate is the body from which the name of the whole class is derived. It is obtained by grinding the seeds of the black mustard in water, and distilling the liquid after it has stood for a certain time. The seeds contain a glucoside which is of a rather unusual kind, since it is a potassium salt, potassium myronate. This glucoside breaks up under the influence of a ferment known as myrosin, which is also contained in the seeds, into allyl isothiocyanate, grape sugar, and potassium hydrogen sulphate.

The bodies obtained by the interaction of potassium thiocyanate with acyl halides have been shown to be isothiocyanates. The normal thiocyanates of the acyl radicals do not appear to exist.[1]

FULMINIC ACID

Mercury fulminate was discovered by Howard in 1800. In 1823 Liebig showed that the silver salt has the same composition as silver cyanate. This was the first case of the discovery of two different substances having undoubtedly the same composition; and it was to designate this phenomenon that Berzelius invented the word isomerism.

Mercury fulminate is formed by the action of alcohol on a solution of mercury in excess of nitric acid. The constitution of the salt has long been a matter of great uncertainty. It is extraordinarily reactive, and very explosive, which made the investigation more difficult. Moreover it has not been found possible, even up to the present time, to obtain a stable volatile derivative of fulminic acid,[2] so that its molecular weight can only be inferred from indirect evidence. For a long time the accepted view was that of Divers and others, that the molecule of the acid contains two atoms of carbon, so that it must be written $H_2C_2N_2O_2$. This view was based on its formation from ethyl alcohol, and on the fact that when treated with bromine or iodine it yields compounds containing two carbon atoms in the molecule. On this assumption the most various structures have been erected for it. Kekulé suggested that it was nitro-acetonitrile, $CH_2NO_2{\cdot}CN$. This was soon abandoned, and as a matter of fact this body has recently been prepared,[3] and is found to be a fairly stable oil of rather high boiling-point. Another suggestion is that it is glyoxime peroxide, $\begin{matrix}HC{=}\!\!=CH\\ NO\cdot ON\end{matrix}$, or more probably $\begin{matrix}HC{=}\!\!=CH\\ N{-}O{-}N{>}O\end{matrix}$; but this has also been made,[4] and though it resembles fulminic acid in some respects, it has been proved to be different from it. The fact that fulminic acid, like the oximes, yields hydroxylamine when treated with hydrochloric acid, showed that it must contain the group :NOH, and hence Steiner suggested the formula $\begin{matrix}C{=}NOH\\ \|\\ C{=}NOH\end{matrix}$, which was generally accepted some years ago.

The overthrow of this and all other two-carbon formulae, and the final

[1] Dixon, Taylor, *J. C. S.* **1908**. 684.

[2] Biddle, *Am. Ch. J.* **33**. 60 (*C.* **05**. i. 590), believes that he has obtained methyl fulminate, $CH_3O{\cdot}N{=}C$, as a liquid boiling at 50–60°, with a strong isonitrile smell; but it was too unstable to admit of further investigation.

[3] Steinkopf, Bohrmann, *Ber.* **41**. 1044 (1908).

[4] Jovitschitsch, *Ann.* **347**. 233 (1906).

establishment of our knowledge of fulminic acid on a firm basis, is due to the work of Nef.[1] He showed in the first place that all the evidence was in favour of its containing only one carbon atom in the molecule. Its decomposition-products are nearly always one-carbon bodies. It is formed, as we have seen, by treating sodium nitromethane with mercuric chloride, and if treated with nitrous acid it is converted[2] into methyl-nitrolic acid, $H\cdot C\langle^{NO_2}_{NOH}$. If we take it as proved that there is only one carbon atom in the molecule, and also consider the fact that on treatment with hydrochloric acid it gives hydroxylamine, only one formula is possible, namely H·O·N=C″. The real reason which prevented the earlier investigators from adopting such a one-carbon structure as this was their unwillingness to admit the existence of a dyad carbon atom. But this objection has been removed by Nef's other work on dyad carbon, and he has been able to show that his formula is alone capable of explaining the very remarkable reactions of fulminic acid ; while all subsequent work on these bodies has only served to confirm his views.

The formula explains the production of the salt from mercury nitromethane by 'intramolecular oxidation':—

$$CH_2{=}N\langle^{O}_{Ohg} = C{=}N\cdot Ohg + H_2O. \quad (hg = \tfrac{1}{2}\,Hg.)$$

It represents it as an oxime, and hence accounts for the formation of hydroxylamine on hydrolysis. Further, it represents it as the oxime of carbon monoxide, containing therefore, like carbon monoxide itself, a dyad carbon atom. Now the dyad carbon atom, wherever it occurs, is always extraordinarily active, as we have seen in the case of the isocyanogen compounds. It has the strongest tendency to pass into the tetrad condition, and will do so if it possibly can, even at the cost of forming very unstable compounds. The formation of methyl-nitrolic acid is the simplest case of this:—

$$H\cdot O\cdot N{=}C + HNO_2 = H\cdot O\cdot N{=}C\langle^{H}_{NO_2}.$$

A similar reaction takes place with hydrochloric acid. If sodium fulminate is treated with this acid at 0°, the fulminic acid first liberated forms an addition-compound with the hydrochloric acid, the carbon becoming tetravalent:—

$$HO\cdot N{=}C'' + HCl = HO\cdot N{=}C\langle^{H}_{Cl}.$$

This body is the oxime of formyl chloride, $O{=}C\langle^{H}_{Cl}$, and is therefore called formyl chloride oxime. Its properties are remarkable. It forms large colourless crystals, which are rapidly and completely volatile at the ordinary temperature. If it is allowed to stand in the cold it soon begins to decompose, and the decomposition when once it has set in proceeds with almost explosive violence, and with the evolution of enormous quantities of heat. In this reaction carbon monoxide is evolved, and a residue left behind consisting mainly of hydroxylamine hydrochloride. That is, the oxime dissociates into fulminic acid and

[1] *Ann.* **280**. 303 (1894). [2] Palazzo, *C.* **07**. ii. 135.

hydrochloric acid, and the former is hydrolysed by the latter in the normal manner.

The structure of formyl chloride oxime is proved by its behaviour on treatment with aniline in ethereal solution, when it gives a precipitate of phenyl isuretin :—

$$HO{\cdot}N{=}C\langle^{H}_{Cl} + \phi NH_2 = HO{\cdot}N{=}C\langle^{H}_{NH\phi} = HO{\cdot}NH{\cdot}C\langle^{H}_{N\phi}.$$

The formula of the product was shown by synthesizing it from isuretin and aniline :—

$$HO{\cdot}NH{\cdot}C\langle^{H}_{NH} + H_2N\phi = HO{\cdot}NH{\cdot}C\langle^{H}_{N\phi} + NH_3.$$

If silver fulminate is suspended in water and one equivalent of hydrochloric acid added, part of the silver is precipitated as silver chloride, but a clear solution remains which contains both silver and chlorine. The first effect of the hydrochloric acid is to add on to the dyad carbon, forming the silver salt of the oxime $AgO{\cdot}N{=}C\langle^{H}_{Cl}$. This soluble compound is partly decomposed by more of the acid to form silver chloride and the free oxime, but not wholly. This is a remarkable proof of the activity of the dyad carbon ; it holds the chlorine so firmly that it cannot react with the silver. It is also a strong argument in favour of Nef's view that when a metallic cyanide reacts with an alkyl halide to form a nitrile, an intermediate additive compound is formed with the carbon tetrad ; for we have here an example of an additive compound of this type which is capable of more or less permanent existence.

It has recently [1] been discovered that fulminic acid can exist in the free state, though it is too unstable to be isolated. It was shown by Scholvien [2] that if a solution of potassium fulminate is treated with excess of sulphuric acid, ether extracts from it a substance which with silver nitrate forms silver fulminate. This he assumed to be free fulminic acid. Nef,[3] on the other hand, argued that it was formyl sulphate oxime, $\overset{HSO_4}{H}\!\!>C{=}NOH$. Wieland and Hess have repeated the work, and have shown that the ethereal solution contains no trace of sulphuric acid, so that Nef's view must be wrong, and the solution must really contain free fulminic acid. They also showed that if the ether is distilled at 0°, the acid goes over with the vapour, and will form silver fulminate in the receiver. Hence the free acid exists in the vapour as well as in the solution. If the solution is allowed to stand, it rapidly polymerizes to metafulminuric acid.

Fulminic acid is easily formed from methyl-nitrolic acid [4] :—

$$HC\langle^{NOH}_{NO_2} = HNO_2 + C{=}NOH,$$

a reaction which, as we have already seen, is reversible. It is also produced in three analogous reactions, from amino-methyl-nitrosolic acid [5] :—

$$H_2N{\cdot}C\langle^{NOH}_{N:O} = H_2O + N_2 + C{=}NOH,$$

[1] Wieland, Hess, *Ber.* **42.** 1346 (1909). [2] *J. pr. Ch.* **32.** 461 (1885).
[3] *Ann.* **280.** 315 (1894). [4] Wieland, *Ber.* **40.** 418 (1907). [5] Wieland, *Ber.* **42.** 820 (1909).

from the hydrochloride of form-oxy-amidoxime[1]:—

$$HC\begin{matrix}\diagup NOH \\ \diagdown NHOH\cdot HCl\end{matrix} = NH_2OH\cdot HCl + C{=}NOH,$$

and from the oxidation product of this amidoxime, methyl-nitrosolic acid:—

$$2\ HC\begin{matrix}\diagup NOH \\ \diagdown N{:}O\end{matrix} = HON{=}NOH + 2\ C{=}NOH.$$

Nef has shown that there is an extraordinary resemblance between fulminic and hydrocyanic acids, which is explained if we suppose that one is the hydride and the other the hydroxide of isocyanogen: H·N=C, HO·N=C. The older writers state that when a fulminate is treated with hydrochloric acid, prussic acid is formed, though they were not able to isolate it. They were misled by the smell, which is very like that of prussic acid. This smell is not that of formyl chloride oxime (the actual product), but is evidently due to traces of fulminic acid, arising from a slight dissociation of the oxime. It can scarcely be distinguished from the smell of prussic acid.

But the resemblance goes further than this. The fulminates are nearly if not quite as poisonous as the cyanides, and their physiological effects are identical. Again, Nef has succeeded in preparing sodium ferrofulminate, $Na_4Fe(ONC)_6$, by treating an alkaline solution of sodium fulminate with ferrous sulphate. This is strictly analogous to sodium ferrocyanide, which should really be written $Na_4Fe\ (NC)_6$. The solution of the ferrofulminate gives none of the reactions of iron, and on evaporation the salt crystallizes out in large yellow needles. It resembles the ferrocyanide in giving a colour with ferric chloride, which in this case is purple; and Nef states that this test is very delicate. It differs, however, from the ferrocyanide in being very unstable, breaking up into its constituents sodium fulminate and ferrous fulminate at once on losing its water of crystallization, and refusing to form the corresponding ferrofulminic acid on treatment with mineral acids. Also it will not form the ferrifulminate when oxidized with bromine water.

Nef's views on the structure of the fulminates have received strong confirmation from the work of Scholl and his pupils[2] on the syntheses effected by means of mercury fulminate and aluminium chloride. They find that if benzene is treated with mercury fulminate and a mixture of anhydrous and hydrated aluminium chloride, it is converted into benzaldoxime. This reaction is easily explained by Nef's formula of the fulminates, but by no other. The water of the hydrated aluminium chloride liberates a certain quantity of hydrochloric acid, and this combines with the fulminic acid which it sets free from the mercury salt to give formyl chloride oxime. This then reacts with the benzene in the normal manner of the Friedel-Crafts synthesis, forming an oxime:—

$$HO\cdot N{=}C\begin{matrix}\diagup H \\ \diagdown Cl\end{matrix} + C_6H_6 = HO\cdot N{=}C\begin{matrix}\diagup H \\ \diagdown C_6H_5\end{matrix} + HCl.$$

The yield under favourable conditions amounts to 70 per cent. The presence of the hydrated aluminium chloride is necessary to the reaction. If it is not used the nitrile is formed instead (up to 80 per cent.). This is not due to a dehydra-

[1] Wieland, Hess, *Ber.* **42.** 4175 (1909).
[2] *Ber.* **32.** 3492 (1899); **36.** 10, 322, 648 (1903).

tion of the oxime by the aluminium chloride, since it was shown that the oxime is practically not converted into the nitrile at all by aluminium chloride. It seems probable that in the absence of water the fulminic acid reacts with the aluminium chloride to give cyanogen chloride, which then changes over into its tautomeric form; and this by the Friedel and Crafts reaction forms the nitrile :—

$$C{=}N{\cdot}OH \longrightarrow C{=}N{\cdot}Cl \longrightarrow Cl{\cdot}C{\equiv}N + C_6H_6 \longrightarrow C_6H_5{\cdot}CN.$$

The conditions of the reaction, which must be very carefully observed, are curious. With benzene the best yield is got by using a mixture of anhydrous and hydrated aluminium chloride corresponding to the formula Al_2OCl_4. But with the homologues of benzene, which favour the formation of the nitrile, the amount of hydrated salt must be increased, up to the composition AlOCl. It is also better to add a certain quantity of aluminium hydrate, but this seems to have only a mechanical action, preventing the solid salt from caking together. A further point is that in order to get the oxime the fulminate must be added first to the benzene, and then the aluminium compounds: while the reverse order must be adopted if the nitrile is wanted. These syntheses can also be carried out with the phenol ethers.

The analogy between fulminic and hydrocyanic acids holds here as well, as is shown by Gattermann's synthesis of the aldimines from phenol ethers on treatment with anhydrous prussic acid and hydrochloric acid in the presence of aluminium chloride (see above, p. 199).

The one thing needful to establish Nef's formula beyond all doubt is a determination of the molecular weight. If it can be shown that fulminic acid contains only one carbon atom in the molecule, we have no alternative but to accept Nef's view as to its structure. A direct determination of this magnitude is impossible, but indirect evidence of great force has recently been adduced,[1] from the electrolytic behaviour of the sodium salt in aqueous solution. The salt can be prepared by treating mercury fulminate in alcohol with sodium amalgam, and is fairly stable. On Nef's theory it is the salt of a monobasic acid NaONC; on any other the acid is dibasic, and the salt $Na_2(ONC)_2$. Now van 't Hoff has shown that the alkaline salts of monobasic acids in fifth to tenth normal solution give a value of the dissociation factor i of about 1·85, and those of dibasic acids about 2·5. From this it follows that if sodium fulminate is NaONC, its apparent molecular weight in solution should be 35, but if it is $Na_2(ONC)_2$, it should be about 52. From the depression of the freezing-point in fifth normal aqueous solution, it was found to be 34·9, agreeing with that required for the monomolecular formula. Again, Ostwald found that the increase in molecular conductivity in passing from $N/_{32}$ to $N/_{1024}$ solution, for the salt of a monobasic acid was from 4 to 8 units, and for that of a dibasic acid about 11. The observed increase for sodium fulminate was 5 units. These results make it certain that the acid is monobasic, and has the formula HONC; and hence Nef's view as to its structure must be adopted.

The reactions which take place in the ordinary method of preparing mercury fulminate by the violent oxidation of ethyl alcohol by a solution of mercury in

[1] L. Wöhler, *Ber.* **38.** 1351 (1905).

nitric acid are obscure and difficult to explain. It has been shown[1] that oxides of nitrogen (fuming nitric acid) must be present; that acetaldehyde gives a much larger yield of fulminate than alcohol; and that one-carbon bodies (methyl alcohol, formaldehyde) and also 3- and 4-carbon compounds give none at all. The explanation has been given by Wieland.[2] He finds that methyl-nitrolic acid, $\begin{matrix}\diagup\!\!\diagdown NOH \\ CH \\ \diagdown\!\!\diagup NO_2\end{matrix}$, can be converted into fulminic acid, as indeed we should expect, since it is the analogue of formyl chloride oxime:—

$$HO{\cdot}N{=}C\begin{matrix}H\\Cl\end{matrix} \quad : \quad HO{\cdot}N{=}C\begin{matrix}H\\NO_2\end{matrix}.$$

It is evident that the alcohol is first oxidized to aldehyde (hence the latter gives the best yield): this is converted by the nitrous acid present into isonitroso-acetaldehyde, and this further oxidized to isonitroso-acetic acid. This last body has been shown[3] to be converted by nitrous fumes (by nitration followed by loss of carbon dioxide) into methyl-nitrolic acid, which reacts with mercuric nitrate to give mercury fulminate:—

$$CH_3{\cdot}CH_2OH \rightarrow CH_3{\cdot}CHO \rightarrow HO{\cdot}N{:}CH{\cdot}CHO \rightarrow HO{\cdot}N{:}CH{\cdot}COOH \rightarrow HO{\cdot}N{:}C(NO_2)COOH \rightarrow HO{\cdot}N{:}C(NO_2)H \rightarrow HO{\cdot}N{:}C.$$

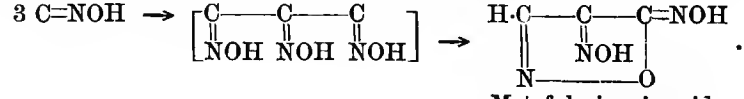
The one-carbon compounds cannot give fulminate, since it is only when the methyl group is united to a strongly negative grouping such as carbonyl that the oxides of nitrogen are able to introduce the isonitroso-grouping into it.

The peculiar reaction of the fulminates with bromine is discussed below (p. 230).

Polymers of Fulminic Acid

Fulminic acid gives rise to a series of polymerization products. If mercury fulminate is boiled with potassium chloride solution, it gives the salt of fulminuric acid, as was discovered by Liebig. This acid[4] has been shown to be nitrocyan-acetamide, $\begin{matrix}N{\equiv}C\\NO_2\end{matrix}\!\!\diagdown CH{\cdot}CO{\cdot}NH_2$; but the mechanism of its formation is obscure, and even its structure is disputed.

The other polymerization products form a continuous series. If the ethereal solution of free fulminic acid, obtained by extracting the acidified solution of the potassium salt with ether, is allowed to stand, a triple polymer, originally known as isocyanuric acid, but now more conveniently termed metafulminuric acid, is produced. This has been shown[5] to be isonitroso-isoxazolone:—

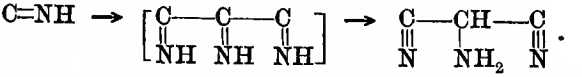


Metafulminuric acid.

This polymerization brings out the resemblance of fulminic and hydrocyanic

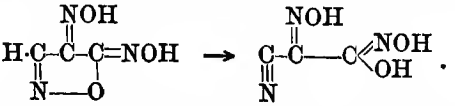
[1] L. Wöhler, Theodorovits, *Ber.* **38.** 1351 (1905). [2] *Ber.* **40.** 418 (1907).
[3] Ponzio, *Gaz.* **33.** i. 510 (1903).
[4] Steiner, *Ber.* **9.** 781 (1876); Conrad, Schultze, *Ber.* **42.** 735; Steinkopf, ib. 2026 (1909).
[5] Wieland, Hess, *Ber.* **42.** 1346 (1909).

acids as compounds of dyad carbon. It is exactly analogous to the polymerization of hydrocyanic acid in presence of alkali to amino-malonitrile :—

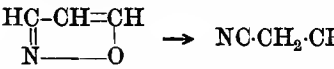


The corresponding compounds of tetrad carbon, the nitriles, cyanates, isocyanates, and the nitrile-oxides, all polymerize to form a symmetrical 6-ring, as in cyamelide and cyanuric acid.

When metafulminuric acid is warmed with water, it goes over into cyan-isonitroso-acethydroxamic acid, whose constitution was established by Nef :—



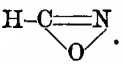
This is a not unusual rearrangement of the isoxazole ring, and occurs, for example, with isoxazole itself, which is converted by alkalies into cyan-acetaldehyde [1] :—



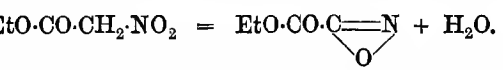
Finally, the hydroxamic acid derivative can be converted into the so-called isofulminuric acid of Ehrenberg,[2] whose constitution is still unknown.

NITRILE-OXIDES

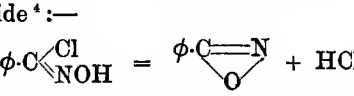
The nitrile-oxides, of which until recently very little was known, are derivatives of the third isomer of cyanic acid, which probably has the structure



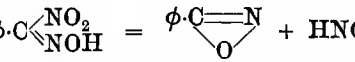
When silver nitrite acts on bromacetic ester, a small quantity of the so-called oxalic ester nitrile-oxide is formed,[3] by loss of water from the primary product, nitro-acetic ester :—



The analogous benzonitrile-oxide is obtained by the action of soda on benzhydroxamic chloride [4] :—



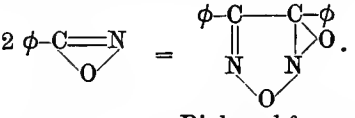
or by the spontaneous decomposition of benzonitrolic acid [5] :—



Their reactions have been further examined by Wieland.[6] They polymerize, with extraordinary ease, in three different ways. By themselves, or in neutral solution, they form double polymers of the class previously known as glyoxime-

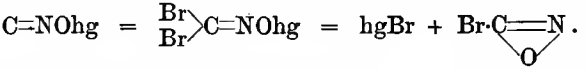
[1] Claisen, *Ber.* **36.** 3666 (1903).
[2] *J. pr. Ch.* [2] **30.** 38 (1884).
[3] Scholl, Schofer, *Ber.* **34.** 862, 870 (1901).
[4] Werner, Buss, *Ber.* **27.** 2199 (1894).
[5] Wieland, Semper, *Ber.* **39.** 2522 (1906).
[6] *Ber.* **40.** 1667 (1907); **42.** 803 (1909).

peroxides, which, however, have now been shown[1] to be 5-ring compounds, and are called furoxanes:—

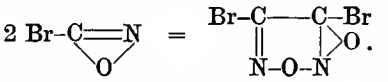


Diphenyl-furoxane.

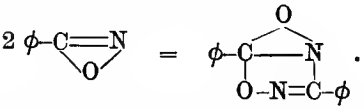
This polymerization enables us to explain the singular action of bromine on silver or mercury fulminate, whereby dibromo-furoxane (dibromo-glyoxime-peroxide) is formed.[2] The bromine first attaches itself to the dyad carbon, as hydrochloric acid does, and then the product loses mercuric bromide:—



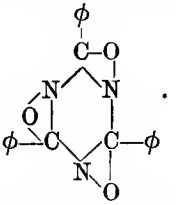
This gives bromo-formonitrile oxide, which will at once polymerize to the dibromo-furoxane which is actually obtained:—



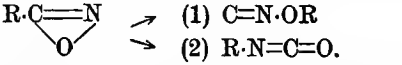
In presence of hydrochloric acid two molecules of benzonitrile-oxide combine in a different way, giving dibenz-oxo-azoxime:—



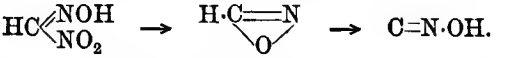
Finally, in alkaline solution they give another series of polymers, the trifulmines, which differ from the first two in readily going back to the monomolecular nitrile-oxides, with which they are identical in most of their reactions. These bodies are probably triple polymers, and their formulae are written by Wieland, on the analogy of cyanuric acid, thus:—



The reactions of the nitrile-oxides fall into two classes, depending on a preliminary isomeric change either into a fulminate or into an isocyanate:—



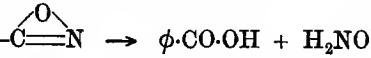
The production of fulminic acid from methyl nitrolic acid evidently takes place through the unstable formonitrile-oxide, which can be isolated as the triple polymer:—



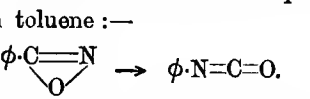
[1] Wieland, Semper, *Ann.* **358.** 36 (1908).

[2] Holleman, *Rec. Trav.* **10.** 77 (1891); Wieland, *Ber.* **42.** 4198 (1909).

If benzonitrile-oxide is treated with hydrochloric acid, it is to some extent hydrolysed to benzoic acid and hydroxylamine, which again indicates its character as a hydroxylamine derivative :—

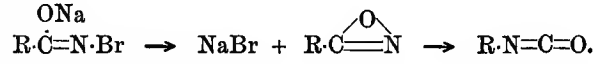


The second type of reaction, leading to an isocyanate, is commoner. Thus the triple polymer of benzonitrile-oxide is converted quantitatively into phenyl isocyanate by heating with toluene :—

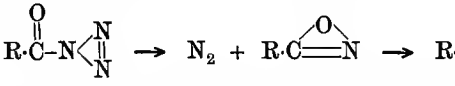


In the same way carbon dioxide and substituted ureas are always found among the products of hydrolysis of these compounds.

This reaction, involving the migration of a hydrocarbon radical from the carbon to a nitrogen doubly linked to it, is obviously analogous to the reactions of Beckmann, Hofmann, and Curtius. In the case of the last two of these, where an isocyanate is known to be formed, it is not an improbable suggestion [1] that the nitrile-oxide is an intermediate product. Thus in the Hofmann reaction we should have :—



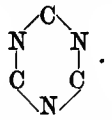
and in the Curtius reaction :—



The peculiar position of these bodies on the line between the hydroxylamine derivatives of carboxylic acids (as shown by their giving hydroxylamine and fulminic acid derivatives) and amine derivatives of carbonic acid (giving isocyanates and their hydrolytic products) is well explained by the oxygen bridge. This has the further advantage over the alternate formula R·C≡N=O, that it accounts for their comparatively saturated character, addition-reactions (apart from polymerization) not taking place readily.

TRICYANOGEN COMPOUNDS

Nearly all cyanogen compounds polymerize with great ease to form trimolecular polymers, which in most cases can readily be reconverted into the simple bodies. The most natural way of accounting for this is to suppose that the three CN groups combine to form a tricyanogen ring, of the form

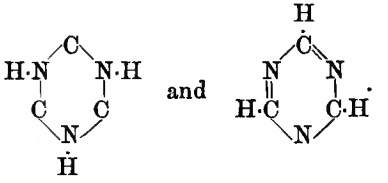


A strict proof of the existence of this ring is still wanting ; but it has been shown that the tricyanogen complex has a symmetrical structure. If cyanuric chloride is treated with ammonia or amines, the chlorine atoms are replaced by NH_2 or substituted NH_2 groups. By regulating the quantities, the replacement

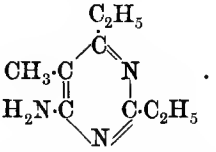
[1] See however Wieland, *Ber.* **42**. 4207. (1909).

may be made to occur in three stages, and by employing successively ammonia, methylamine, and ethylamine, we can replace the three chlorine atoms by amino-, methylamino-, and ethylamino-groups respectively, giving a substance known as methyl-ethyl-melamine $(C_3N_3)(NH_2)(NH{\cdot}CH_3)(NH{\cdot}C_2H_5)$. Now it is found that whatever be the order in which the three groups are introduced, the same product is obtained, proving that the central C_3N_3 nucleus is symmetrical; and this can only be accounted for by assuming the existence of a ring of the form suggested above, which is known as the triazine ring.

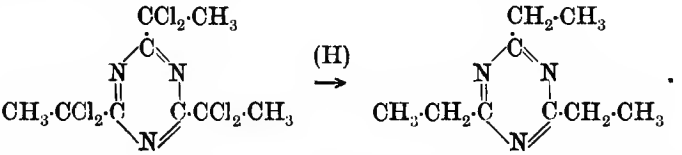
The mother substance of the group, triazine or tricyanogen hydride, has not yet been prepared. It may have two tautomeric formulae:—



The simple derivatives—those which contain no oxygen and only have the hydrogen of the triazine replaced by hydrocarbon groups—must all be derived from the first or second formula, since they are formed by the polymerization of nitriles and not of isocyanides. But, as has been pointed out, the usual product of the polymerization of a nitrile is a cyanalkine, an amino-pyrimidine, such as



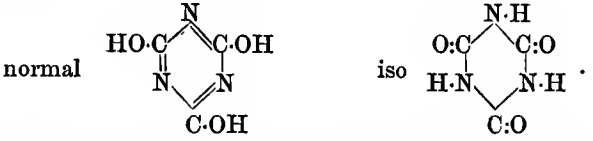
That is to say, instead of the three CN groups forming the ring, one nitrogen is driven outside, while a carbon atom from one of the alkyls takes its place. This is obviously only possible if the nitrile employed has, next to the CN, a carbon atom united to hydrogen. Hence, if a nitrile is used which has no hydrogen on this carbon, the reaction takes a different course, and a triazine (tricyanogen) compound is formed. For instance, benzonitrile polymerizes in presence of sulphuric acid to form triphenyl triazine. In this case a pyrimidine could not be formed without breaking one of the benzene rings. Again, α,α-dichloro-propionitrile condenses to a tricyanogen body which, on reduction, yields triethyl-triazine:—



This is a colourless compound of peculiar smell, melting at 29° and boiling at 193–195°, which, when heated with hydrochloric acid, gives ammonia and propionic acid, i.e. is at once depolymerized and saponified.

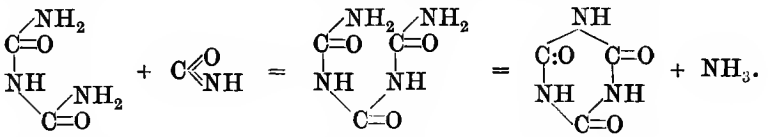
Among the cyanic acid derivatives the formation of tricyanogen compounds

is quite general. Cyanuric acid, $C_3N_3O_3H_3$, the mother substance of this group, is formed by the spontaneous polymerization of cyanic acid, and also by heating urea and many of its derivatives. It can obviously occur in two tautomeric forms, one derived from normal cyanic acid HO·CN, and the other from isocyanic acid H·N=C=O:—



The balance of evidence is on the whole in favour of the iso (imide) structure for the free acid. The tri-N-ester, the derivative of this form, is the product of the action of diazomethane on the acid.[1] Cyanuric acid is a pseudo-acid, and the sodium salt, which is derived from the true acid form, shows by its behaviour that it has the metal attached to oxygen: from which it follows that the free acid must be the imide. The same conclusion has been arrived at by Hartley from the absorption spectra of cyanuric acid and its derivatives.

The acid can also be obtained by heating biuret with cyanic acid:—



It is best prepared by treating cyanuric bromide with water. On heating it breaks up, regenerating cyanic acid.

The chloride and bromide of cyanuric acid may be got by heating the acid with phosphorus pentahalide; but they are more readily obtained by allowing cyanogen halide to stand in the presence of a little halogen or halogen acid. Chattaway has shown that in these bodies the halogen does not behave as if it were attached to nitrogen. Hence they must have the normal structure $Cl{\cdot}\overset{|}{C}{=}N-$, with the halogen on the carbon. They yield cyanuric acid on heating with water.

The esters of cyanuric acid exist in four isomeric forms, as each alkyl group may be attached either to oxygen or to nitrogen, $Alk{\cdot}O{\cdot}\overset{|}{C}{=}N-$ or $Alk{\cdot}\overset{|}{N}-\overset{||}{C}{:}O$. The tri-O-ester and the tri-N-ester have long been known; and Hantzsch[2] has recently prepared the two mixed compounds. The tri-O-ester is obtained from cyanuric bromide and sodium methylate; the di-O-mono-N-ester from silver cyanate and methyl iodide below 0°; the mono-O-di-N-ester from silver cyanurate and methyl iodide at low temperatures: while these bodies if warm give the tri-N-compound. The constitution of these esters is proved by heating them with hydrochloric acid, when only the methyls which are attached to oxygen are saponified. The tri-N-ester can also be obtained by boiling the tri-O-ester with water, when it slowly changes over.

The isomerism of the esters is repeated, at any rate as regards two of them,

[1] Palazzo, Scelsi, *Gaz.* **38**. i. 659 (*C.* **08**. ii. 774).

[2] Hantzsch, Bauer, *Ber.* **38**. 1005 (1905).

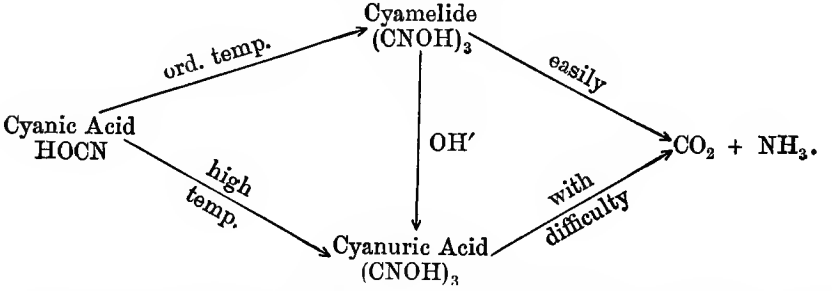
in the mercuric salts, as Hantzsch [1] has shown. If sodium cyanurate is treated with mercuric chloride at 0°, it precipitates the oxygen salt; but at 100° the N-salt is formed. These salts are unfortunately very inactive and quite insoluble, so that their molecular weights cannot be determined, nor the products of their interaction with alkyl iodides; but they are isomeric, and their formulae are sufficiently established by the fact that one of them is decomposed by alkali to form alkaline cyanurate and mercuric oxide, while the other is not affected. This stability to alkali is a general character of compounds containing mercury attached to nitrogen, as for example mercury acetamide. It is remarkable that though by precipitating them at temperatures between 0° and 100° a mixture of the two salts can be obtained, in which there is more of the N-salt the higher the temperature, it is not found possible by any means to convert one salt into the other. The isomeric salts are thus more stable than the isomeric esters. This may be due to the high atomic weight of mercury, which renders it difficult to move.

Such cases of isomeric salts are rare; but the silver salt of benzamide [2] has been obtained in two forms, which are no doubt $\phi\cdot C\langle^{O}_{NHAg}$ and $\phi\cdot C\langle^{OAg}_{NH}$: while the mercury salt of nitroform offers the still more remarkable phenomenon of an actually tautomeric salt, having one structure in ionizing and another in non-ionizing solvents.

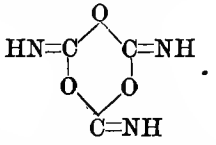
Cyamelide is an obscure polymer of cyanic acid, which may be mentioned here, though it does not belong to the tricyanogen compounds in the strict sense. It is formed by the spontaneous polymerization of anhydrous cyanic acid, and also by the action of carbonyl chloride on ammonia. Its slow production by the polymerization of cyanic acid in the gaseous state has been investigated in great detail by van 't Hoff,[3] and it affords a classical example of the influence of disturbing factors on the rate of gaseous reaction. The cyanic acid vapour was enclosed over mercury, and the rate of reaction followed by means of the change of pressure. It was found that the velocity was affected by the area of the glass surface, being nearly half as great again in a long narrow tube as in a globe. It was also much slower at first than after a certain time had elapsed, and this was shown to be due to the accelerating influence exerted by the layer of cyamelide on the surface of the glass: in fact the change was more than three times as rapid in a vessel whose walls were covered with a layer of cyamelide as in a clean vessel. Both these influences were much diminished if the gas was diluted with air. If these disturbing influences are eliminated, either by observing the initial velocities at various pressures in clean vessels, or by using vessels already coated with cyamelide, it is found that the reaction is approximately trimolecular. The structure of cyamelide was until recently quite unknown, but Hantzsch [4] has been able to throw a certain amount of light upon it. As it is non-volatile and insoluble in the ordinary solvents, its molecular weight cannot be determined directly. But its effect on the freezing-point of pure sulphuric acid (in which it dissolves) shows that its

[1] *Ber.* **35.** 2717 (1902).
[2] Titherley, *J. C. S.* **1897.** 468.
[3] See *Studies in Chemical Dynamics.*
[4] *Ber.* **38.** 1013 (1905).

molecular weight cannot be very high, while the fact that its formation from cyanic acid is a trimolecular reaction indicates that its formula must be $(C_3N_3H_3O_3)_n$. If n was greater than one, we should expect to find that it was very much less active than cyanuric acid, which is not the case: for example, it is much more easily decomposed by sulphuric acid. We may therefore conclude that its formula is probably $C_3N_3H_3O_3$. It is feebly acidic, but gives no salts, and is converted by alkalies into a salt of cyanuric acid. The relations of these bodies are shown in the following scheme:—



Since cyanuric acid cannot be converted into cyamelide directly, but only through cyanic acid, cyamelide cannot have any of the possible pseudo-cyanuric formulae, nor can it be a stereoisomer of cyanuric acid. It cannot in fact have a tricyanogen (triazine) ring at all; nor, since it forms no salts, can it have any group capable of forming a salt directly (as HO·C–N–) or indirectly (as HN–C=O). Since it gives a mercury derivative in which the metal is attached to nitrogen, it must contain imide groups. Hence it must be a polymer not of HO·C≡N but of H·N=C=O, and the three molecules of this must be joined up through oxygen. We thus arrive at the structure:—



This accounts for all the relations described above; in fact cyamelide is related to cyanic acid in the same way as paraldehyde to aldehyde; and hence it is more easily converted than is cyanuric acid into cyanic acid (or carbon dioxide and ammonia) under the influence, for example, of acids.

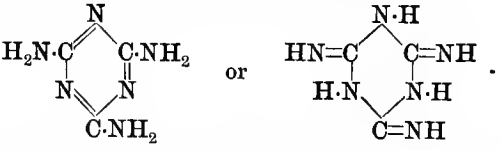
Thiocyanuric Compounds

Corresponding to the cyanuric compounds are a group of the thiocyanuric derivatives, in which the oxygen is replaced by sulphur. They resemble the cyanuric compounds so closely that they need not be described in detail. But they afford another example of the rule which holds generally among bodies exhibiting amide-imide tautomerism: that while in the oxy-derivatives the imide (NH) form is the most stable, both in the free hydrogen compound and in the salts and esters, the reverse is the case among the thio-compounds. Thus both

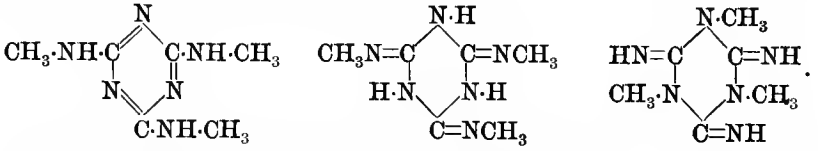
the N- and the O-esters of cyanuric acid are stable, but the former are the more stable, since the normal esters are slowly converted into them on boiling. Among the esters of thiocyanuric acid these relations are reversed. Normal (S-) thiocyanuric esters are easily prepared, while it is doubtful whether the iso (N-) esters exist at all.

Melamines, &c.

As a tribasic acid, cyanuric acid can give a mono-, di-, and triamide; and each of these, like cyanuric acid itself, has two tautomeric forms. The most important of these bodies is the triamide, melamine



It is formed by the action of ammonia on the normal esters of cyanuric or thiocyanuric acid, or better on cyanuric chloride. The symmetrical trialkyl melamines may have three formulae:—



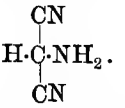
The first and second of these differ only in the position of a hydrogen atom, and are therefore tautomeric, while the third is quite distinct. Accordingly, we find that two series of trialkyl melamines are known. The members of one series are got by acting on thiocyanuric esters or cyanuric chloride with primary amines: on decomposition they give cyanuric acid and primary amines. They therefore possess the first or the second formula. To distinguish them from the compounds of the third type they are called *exo*-trialkyl melamines, since the nitrogen of the amine group is outside the ring. Derivatives of the third form, with the amine nitrogen forming part of the ring, are known as *eso*-melamines. They are obtained by the polymerization of the alkyl cyanamides, and their constitution is proved by their giving on saponification ammonia and isocyanuric esters.

Summary

The following summary of the polymerization products of the different classes of cyanogen compounds may be of use.

Cyanogen forms paracyanogen, of unknown molecular weight and structure.

Hydrocyanic acid on standing in aqueous solution in the presence of a little potassium carbonate gives a triple polymer, which is probably amino-malonic nitrile



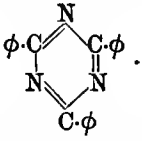
The ordinary nitriles of the fatty series, if treated with sodium in ethereal

solution, yield double polymers which are imino-nitriles: for example, methyl cyanide gives

$$CH_3\cdot C(=NH)\cdot CH_2\cdot CN\,,$$

and when treated with sodium in the absence of a solvent they give cyanalkines, i.e. pyrimidines.

Those fatty nitriles which have no hydrogen attached to the same carbon as the CN, and all aromatic nitriles, give derivatives of the tricyanogen ring: thus benzonitrile gives



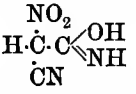
Cyanic acid changes spontaneously into a mixture of cyanuric acid, a tricyanogen or triazine compound, and cyamelide, a body containing a ring of three carbons and three oxygens.

The cyanogen halides give the halides of cyanuric acid on standing. The isocyanic esters give the isocyanuric esters.

Cyanamide on heating is converted into the corresponding cyanuric compound, melamine or cyanuric triamide, and also into a double polymer dicyandiamide, which is cyan-guanidine

$$HN{=}C\begin{matrix}NH_2\\ NH\cdot CN\end{matrix}.$$

Fulminic acid polymerizes spontaneously to an isoxazolone derivative, which changes to cyanisonitroso-acethydroxamic acid: while its salts on boiling in aqueous solution form the salts of fulminuric acid or nitrocyanacetamide:—



Finally, the nitrile-oxides change spontaneously into two classes of double polymers, furoxanes (glyoxime-peroxide) and oxo-azoximes: and also into triple polymers (trifulmines) probably containing the tricyanogen ring.

DIVISION III

COMPOUNDS CONTAINING AN OPEN CHAIN OF TWO OR MORE NITROGEN ATOMS

These compounds fall into two subgroups:—

1. Those containing two, and
2. Those containing more than two nitrogen atoms in the chain.

The second of these subgroups is comparatively unimportant. The first consists of:—

1. The derivatives of hydrazine, $H_2N{\cdot}NH_2$, including the hydrazo-compounds.

2. The diazo- and azo-compounds, derived from the hypothetical diimide, HN=NH.

3. The oxyazo-compounds, which, though strictly speaking ring bodies, containing the group $\begin{matrix}-N-N-\\ \diagdown\diagup \\ O\end{matrix}$, are more conveniently dealt with here.

4. The nitroso- and nitro-amines, $R{\cdot}N\langle^{H}_{NO}$ and $R{\cdot}N\langle^{H}_{NO_2}$.

CHAPTER X

HYDRAZINE DERIVATIVES

These may be divided into three classes:—

1. Purely aliphatic derivatives.

2. Purely aromatic and mixed derivatives, which have either only one aromatic group, or two attached to the same nitrogen.

3. Compounds containing aromatic groups attached to both nitrogen atoms. These are the hydrazo-compounds, such as hydrazobenzene, $\phi\cdot NH\cdot NH\cdot\phi$. Their behaviour is so different from that of the other members of the group that they must be dealt with separately.

FATTY HYDRAZINES

The primary alkyl-hydrazines may be obtained by the action of alkyl halides on free hydrazine, or from the mono- or symmetrical di-alkyl ureas by conversion into nitroso-compounds, and reduction with zinc and acetic acid to hydrazine-ureas or semicarbazides, which are then hydrolysed with fuming hydrochloric acid:—

$$\begin{array}{l} CO\langle NH\cdot Et \\ \quad\ NH\cdot Et \end{array} \rightarrow \begin{array}{l} CO\langle N\langle NO \\ \quad\ NH\cdot Et \end{array} \rightarrow \begin{array}{l} CO\langle N\langle NH_2 \\ \quad\ NH\cdot Et \end{array} \rightarrow \begin{array}{l} NH_2 + CO_2 \\ NHEt \\ +\,NH_2\cdot Et \end{array}.$$

They are very hygroscopic, strongly basic liquids. They smell like ammonia, and are corrosive, rapidly destroying cork. When warmed with potassium pyrosulphate, $K_2S_2O_7$, they give salts of the hydrazine sulphonic acids, such as $Et\cdot NH{-}N\langle^{H}_{SO_3K}$. If this body, the potassium salt of monethyl-hydrazine sulphonic acid, is oxidized with mercuric oxide, it is converted into diazo-ethane-sulphonic acid, $C_2H_5\cdot N{=}N\cdot SO_3K$, one of the very few known instances of a fatty diazo-compound of the aromatic or true diazo type.

The secondary fatty hydrazines were obtained by Emil Fischer by the reduction of secondary nitrosamines:—

$$Et_2N{-}N{:}O \rightarrow Et_2N{-}NH_2.$$

They may also be obtained by the direct action of alkyl iodides on hydrazine hydrate. In this reaction it has been shown that the alkyl groups attach themselves only to one of the two nitrogen atoms: the products, for example, from hydrazine and methyl iodide being $CH_3\cdot NH{-}NH_2$, $(CH_3)_2N{-}NH_2$, and finally $(CH_3)_3NI{-}NH_2$.[1]

The secondary alkyl-hydrazines, like the primary, are strongly basic hygro-

[1] Harries, Haga, *Ber.* **31.** 56 (1898).

scopic liquids, which are easily soluble in water. Nitrous acid converts them into secondary amines and nitrous oxide:—

$$\begin{matrix}Et_2N\\|\\NH_2\end{matrix} + \begin{matrix}HO\\|\\O:N\end{matrix} = H_2O + Et_2NH + N_2O.$$

Like all hydrazines they are easily oxidized, and hence are strong reducing agents. Mercuric oxide converts them into tetrazones, such as $Et_2N{-}N{=}N{-}NEt_2$, which are strongly basic liquids.

AROMATIC HYDRAZINES

The aromatic hydrazine derivatives were the first to be discovered, and are by far the most important. Our knowledge of them, as of the fatty compounds, is mainly due to Emil Fischer. The first member of the group was prepared by Strecker and Römer in 1871, by the action of potassium hydrogen sulphite on diazobenzene nitrate:—

$$\phi{\cdot}N_2{\cdot}NO_3 + KHSO_3 \rightarrow \phi NH{-}NHSO_3K.$$

In 1875 Fischer showed that this body on boiling with hydrochloric acid gave phenyl-hydrazine hydrochloride, and by treating this with alkali he prepared phenyl-hydrazine itself, one of the most important reagents in the whole of organic chemistry.

Formation

The primary and secondary compounds are both obtained from the corresponding amines by replacing one hydrogen attached to nitrogen by NH_2, and in both cases by treatment with nitrous acid and subsequent reduction. With the primary amines the diazo-compounds are first produced, and these can then be reduced in three ways:—

1. With stannous chloride in hydrochloric acid solution, giving the hydrazine hydrochloride directly.

2. They can be coupled with potassium hydrogen sulphite, forming the diazo-sulphonate $\phi{\cdot}N{=}N{\cdot}SO_3K$, and then reduced with excess of sulphite, or better with zinc dust and acetic acid, to the hydrazine-sulphonate

$$\phi{\cdot}NH{-}NH{\cdot}SO_3K,$$

which is subsequently hydrolysed by boiling with acids.

3. The diazo-compound is coupled with an amine to form a diazoamino-body, which is then split by reduction:—

$$\phi{\cdot}N{=}N{-}NH{\cdot}\phi + 4\,H = \phi{\cdot}NH{-}NH_2 + H_2N{\cdot}\phi.$$

4. They may also be obtained[1] directly from the phenols (and still more easily from the naphthols) by heating them in aqueous solution with hydrazine sulphite and excess of hydrazine hydrate:—

$$Ar{\cdot}OH + H_2N{-}NH_2 = Ar{\cdot}NH{-}NH_2 + H_2O.$$

This reaction corresponds exactly to the conversion of phenols (and more easily naphthols) into amines.

5. The less important secondary hydrazines are prepared by reducing the nitrosamines with sodium amalgam, or better with zinc and acetic acid in cold alcoholic solution.

[1] Franzen, *J. pr. Ch.* [2] **76**. 205 (*C.* **07**. ii. 1337).

Properties of the primary and secondary aromatic hydrazines

They are colourless liquids or solids, of a feebly aromatic smell, which are easily soluble in alcohol and ether, but only slightly in water, and scarcely at all in concentrated alkali. They are decided monacid bases, forming salts with mineral and some organic acids. Unlike the primary fatty hydrazines they will not form salts with two equivalents of acid, but only with one. Secondary aromatic hydrazines, such as $\phi_2N{-}NH_2$, will form salts with one equivalent of acid, but these are partially decomposed by water. This is like the behaviour of the secondary aromatic amines, and is a sign of the negative character of the phenyl group. It is practically certain that it is only the NH_2 group which takes part in the formation of these salts. On the other hand, the hydrogen of the NH group in phenyl-hydrazine can be replaced by an alkali metal. Sodium dissolves in phenyl-hydrazine, evolving ammonia and producing aniline. That is, the hydrogen driven out from the first molecule of phenyl-hydrazine reduces a second molecule. On evaporating off the aniline, the sodium compound, $\phi{\cdot}NNa{\cdot}NH_2$, remains as a yellow-red transparent mass, absorbing moisture from the air to form sodium hydrate and phenyl-hydrazine, and giving with ethyl iodide unsymmetrical ethyl-phenyl-hydrazine, $\phi EtN{-}NH_2$.

The aromatic hydrazines are very easily oxidized. It is probable that the first oxidation product of a primary hydrazine is a diazo-compound. Phenyl-hydrazine sulphate can be partially converted by mercuric oxide into benzene diazonium sulphate, $\phi{\cdot}N{=}N{\cdot}SO_4H$. Chattaway has shown[1] that all primary aromatic hydrazines are oxidized by chlorine at −15°, or by bromine in acetic acid solution, to give diazo-compounds; and he suggests the following series of reactions to account for the change:—

$$\begin{matrix} R{\cdot}N{\cdot}H \\ | \\ H{\cdot}N{\cdot}H \end{matrix} \rightarrow \begin{matrix} R{\cdot}N{\cdot}Cl \\ | \\ H{\cdot}N{\cdot}Cl \end{matrix} \rightarrow \begin{matrix} R{\cdot}N{\cdot}Cl \\ \| \\ N \end{matrix} + HCl.$$

Further oxidation[2] by means of copper sulphate or ferric chloride, or by bromine in presence of alkali, or even by atmospheric air, especially in the presence of alkali, removes all the nitrogen as nitrogen gas, while the aromatic radical is reduced to the hydrocarbon:—

$$Ar{\cdot}NH{-}NH_2 + O = Ar{\cdot}H + N_2 + H_2O.$$

This reaction may be used for determining a hydrazine quantitatively; and it also affords an indirect means of replacing the diazo-group by hydrogen. Chattaway[3] explains it in a similar way to the formation of a diazo-compound:—

$$\begin{matrix} R{\cdot}N{\cdot}H \\ | \\ H{\cdot}N{\cdot}H \end{matrix} \rightarrow \begin{matrix} R{\cdot}N{\cdot}H \\ | \\ H{\cdot}N{\cdot}OH \end{matrix} \rightarrow \begin{matrix} R \\ | \\ H \end{matrix} + \begin{matrix} N \\ \| \\ N \end{matrix} + \begin{matrix} H \\ | \\ OH \end{matrix}.$$

The intermediate compounds assumed in these reactions have not, however, been isolated.

Secondary aromatic hydrazines behave differently. Gentle oxidation, as in

[1] *J. C. S.* **1908.** 852.

[2] Chattaway, *J. C. S.* **1907.** 1323; **1909.** 1065.

[3] *J. C. S.* **1908.** 270.

the case of the fatty compounds, gives the tetrazones $Ar_2N{-}N{=}N{-}NAr_2$: while a stronger oxidizing agent converts them into nitrogen and secondary amines:—

$$2\,Ar_2N{-}NH_2 + O = 2\,Ar_2NH + N_2 + H_2O.$$

An exception to this rule, which otherwise holds both for fatty and for aromatic derivatives, is presented by dibenzal-hydrazine, $(\phi{\cdot}CH_2)_2N{-}NH_2$.[1] When this is oxidized by mercuric oxide, it does not give a tetrazone but loses its nitrogen and forms dibenzyl:—

$$\begin{matrix}\phi{\cdot}CH_2\\ \phi{\cdot}CH_2\end{matrix}\!\!>\!N{-}NH_2 + O = \begin{matrix}\phi{\cdot}CH_2\\ |\\ \phi{\cdot}CH_2\end{matrix} + N_2 + H_2O.$$

In the elimination of the nitrogen, and the union of the two groups attached to it, this reaction is exactly similar to the oxidation of phenyl-hydrazine to nitrogen and benzene.

The hydrazines can be reduced, though not easily, and then always split between the two nitrogen atoms, giving ammonia and an amine.

Nascent nitrous acid acts on the primary hydrazines at low temperatures to form very unstable nitroso-derivatives,[2] such as $\phi{\cdot}N{<}\begin{matrix}NH_2\\ NO\end{matrix}$, which on gentle warming with alkali lose water and pass into azides, $\phi{\cdot}N{<}\begin{matrix}N\\ \|\\ N\end{matrix}$.

When heated with fuming hydrochloric acid to 200°, phenyl-hydrazine is converted into *p*-phenylene diamine:—

$$C_6H_5{\cdot}NH{-}NH_2 = C_6H_4(NH_2)_2,$$

the usual migration of a substituent from the NH_2 of an aniline to the ring.

1,2,4-dinitro-phenyl-hydrazine is remarkable for the extraordinary ease with which it is acetylated.[3] It is sufficient to warm it with even highly diluted aqueous acetic acid to obtain the acetyl derivative $C_6H_3(NO_2)_2{\cdot}NH{-}NH{\cdot}CO{\cdot}CH_3$.

The mono-alkyl derivatives of phenyl-hydrazine are of two kinds, the symmetrical (β) and the unsymmetrical (α). The α or unsymmetrical are got from the mono-alkyl-anilines by conversion into nitrosamines and reduction; or from sodium phenyl-hydrazine and alkyl iodide. If phenyl-hydrazine itself is treated with alkyl bromide, a mixture of the α- and β-alkyl derivatives is obtained. To separate the β, the mixed product is oxidized with mercuric oxide: the α-body is thus converted into the unstable basic tetrazone, while the β- (symmetrical) gives a mixed azo-compound, as $\phi{\cdot}N{=}N{\cdot}Et$, which, from its volatility and indifference to acids, can easily be separated and re-reduced.

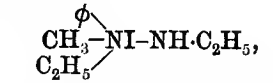
The dialkyl derivatives are got from the α-mono-alkyls in the following manner. The mono-derivative is converted into the formyl-hydrazide by heating with formic acid: the sodium derivative of this is then treated with alkyl iodide, which gives the dialkyl compound, and this on saponification gives the dialkyl-aryl-hydrazine:—

$$\begin{matrix}\phi\\ CH_3\end{matrix}\!\!>\!N{-}NH_2 \rightarrow \begin{matrix}\phi\\ CH_3\end{matrix}\!\!>\!N{-}N{<}\begin{matrix}H\\ CHO\end{matrix} \rightarrow \begin{matrix}\phi\\ CH_3\end{matrix}\!\!>\!N{-}N{<}\begin{matrix}Na\\ CHO\end{matrix} \rightarrow$$

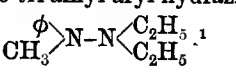
$$\begin{matrix}\phi\\ CH_3\end{matrix}\!\!>\!N{-}N{<}\begin{matrix}Et\\ CHO\end{matrix} \rightarrow \begin{matrix}\phi\\ CH_3\end{matrix}\!\!>\!N{-}N{<}\begin{matrix}Et\\ H\end{matrix}.$$

[1] Busch, Weiss, *Ber.* **33.** 2701 (1900). [2] Cf. Thiele, *Ber.* **41.** 2806 (1908).
[3] Curtius, Mayer, *J. pr. Ch.* [2] **76.** 369 (*C.* **08.** i. 125).

These bodies, when boiled with alkyl halide, are mainly converted into the quaternary azonium compounds, as



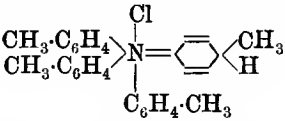
but also to some extent into the tri-alkyl-aryl-hydrazines, such as


[1]

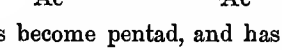
Tetra-aryl-hydrazines

Tetra-phenyl-hydrazine was first obtained[2] by the action of iodine on the sodium derivative of diphenylamine, $\phi_2N{\cdot}Na$, but it and its analogues can be prepared more simply by the oxidation of the diarylamines with lead dioxide or potassium permanganate.[3]

These bodies are remarkable for giving brilliant colours with mineral acids; in fact it is to the production of tetra-phenyl-hydrazine that the blue colour formed in the diphenylamine test for nitric acid is due. These colours do not depend, as was at first supposed, on the splitting of the molecule between the two nitrogen atoms, since under proper conditions the hydrazine can be recovered unchanged. The coloured bodies are therefore coloured salts of the colourless hydrazines. Similar coloured compounds (not double salts) are formed by the addition of the halides of phosphorus, tin, iron, aluminium, and zinc. To account for their colour Wieland suggests[4] that they contain a quinoid ring, and are in fact quinol derivatives: for example, the body obtained from tetra-tolyl-hydrazine and hydrochloric acid may have the formula :—

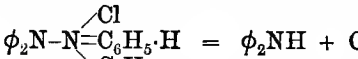


At first this seems impossible, since the quinols have no colour. But quinone diimine, $HN{=}C_6H_4{=}NH$, is itself colourless, while its derivatives of the type



in which the nitrogen has become pentad, and has no hydrogen attached to it, are brilliantly coloured; and we may well suppose that a similar change would produce a coloured compound from a colourless quinol.

These coloured derivatives are especially stable in the case of tetra-tolyl-hydrazine, and it is to be noticed that the stability of the quinols themselves is greatly increased by the presence of a para-methyl group. In the case of tetra-phenyl-hydrazine they soon decompose and lose their colour. The compound splits between the two nitrogen atoms, no doubt primarily thus:—



[1] For a remarkable case of stereo-hindrance in the reaction of the hydrazines with the chloro-fatty acids see Busch and Meussdorffer, *J. pr. Ch.* [2] **75.** 1035 (*C.* **07.** i. 121).

[2] Chattaway, Ingle, *J. C. S.* **1895.** 1090. [3] Wieland, Gambarjan, *Ber.* **39.** 1499 (1906).

[4] *Ber.* **40.** 4260 (1907).

The diphenylamine can actually be isolated; the second half of the molecule decomposes further,[1] giving mainly a diphenylamine derivative:—

$$\phi_2N{\cdot}Cl + H{-}C_6H_4{-}NCl{\cdot}\phi \longrightarrow HCl + [\phi_2N{-}C_6H_4{-}NCl\phi \longrightarrow]$$

$$\phi_2N{-}C_6H_4{-}N{-}C_6H_4Cl.$$

ACID HYDRAZIDES

These bodies are derived from the acids by replacing the hydroxyl by the hydrazine residue, as in $CH_3{\cdot}C\langle^{O}_{NH-NH\phi}$. They thus correspond to the amides. They can be obtained from inorganic as well as organic acids.

Thionyl-phenyl-hydrazone, $\phi NH{-}N{=}S{=}O$, is a kind of dihydrazide of sulphurous acid. If sulphur dioxide is passed into a solution of phenyl-hydrazine in benzene, the additive compound $(\phi NH{-}NH_2)_2{\cdot}SO_2$ is precipitated; and this on heating loses water to give the thionyl-hydrazone, a very stable substance which is volatile without decomposition in steam, but is easily broken up by alkalies, re-forming phenyl-hydrazine and potassium sulphite. The hydrazido-sulphonic acids, as $\phi NH{-}NH{\cdot}SO_3H$, which are intermediate products in the reduction of diazobenzene-sulphonic acid, are half-hydrazides of sulphuric acid.

The hydrazides of the fatty acids are of two kinds, α and β. In the α the acyl is attached to the same nitrogen as the phenyl; in the β or symmetrical it is on the other nitrogen atom.

The α (unsymmetrical) hydrazides may be obtained by the action of an acid chloride or anhydride on sodium phenyl-hydrazine, or by treating β-acet-phenyl-hydrazine with an acid chloride, which gives an α-β-di-acyl compound, $\phi{\cdot}N(CO{\cdot}R){-}NH{\cdot}CO{\cdot}CH_3$, and then boiling with dilute sulphuric acid, which splits off the β-acyl group, and leaves the α- untouched. The α-compounds are distinguished from the β- by not giving the so-called Bülow reaction—a colour with a trace of ferric chloride in concentrated sulphuric acid.

The β- or symmetrical hydrazides are the product of the direct action of phenyl-hydrazine on the acid chlorides, anhydrides, or amides. With one or two exceptions, such as p-tolyl-hydrazide, they give a red or violet colour in the Bülow reaction.

Mercuric oxide oxidizes them in chloroform solution to give red unstable bodies, which evolve nitrogen and are apparently diazo-compounds, such as $\phi{\cdot}N{=}N{\cdot}CO{\cdot}CH_3$.

Many acids react so readily that even on warming with a solution of phenyl-hydrazine in acetic acid they precipitate the hydrazide. This is particularly the case with the highly oxidized acids of the sugars, where this reaction affords a valuable method of separation, as the hydrazides are easily purified, being only slightly soluble, and can then be broken up again into their components by boiling with baryta.

[1] Wieland, *Ber.* **41.** 3478 (1908).

HYDRAZONES

These are among the most important derivatives of phenyl-hydrazine and its analogues. They were discovered by Emil Fischer in 1883. They are of great value for characterizing compounds containing the carbonyl group. They are produced, as a rule, very easily—generally by warming the carbonyl compound with free phenyl-hydrazine in acetic acid solution—when the two condense with the elimination of a molecule of water :—

$$\begin{matrix}R\\R_1\end{matrix}\!\!>\!C{=}O + H_2N{-}NH\phi = \begin{matrix}R\\R_1\end{matrix}\!\!>\!C{=}N{-}NH\phi + H_2O.$$

The rate of formation of the phenyl-hydrazones of a variety of ketones in a variety of solvents has been investigated by Petrenko-Kritschenko.[1] The results are not easy to reduce to a system, but the general conclusions are (1) that the formation is most rapid in acetic acid solution, the other solvents coming in the order ligroin (hexane)—nitrobenzene—benzene, the last being the slowest ; and (2) that the ring ketones, such as hexamethylene ketone, are, except in acetic acid solution, much more rapidly acted on than the open-chain compounds.

The phenyl-hydrazones may conceivably have any one of the three formulae :—

I. $\begin{matrix}R\\R_1\end{matrix}\!\!>\!C{=}N{-}NH\phi.$ II. $\begin{matrix}R\\R_1\end{matrix}\!\!>\!C\!<\!\begin{matrix}NH\\|\\N\phi\end{matrix}.$ III. $\begin{matrix}R\\R_1\end{matrix}\!\!>\!C\!<\!\begin{matrix}H\\N{=}N\phi\end{matrix}.$

Formula III is excluded by the fact that ethane-azo-benzene, $\phi N{=}N{\cdot}CH_2{\cdot}CH_3$, which has this structure, and is obtained by oxidizing ethyl-phenyl-hydrazine with mercuric oxide, is different from the phenyl-hydrazone of acetaldehyde. Formula II is impossible because the unsymmetrical secondary hydrazines, $RR_1N{-}NH_2$, also form hydrazones, the body obtained from benzaldehyde and unsymmetrical phenyl-ethyl-hydrazine, $\phi EtN{-}NH_2$, which must have the structure I, being identical with that got by ethylating benzaldehyde-phenyl-hydrazone. We are therefore left with the first as the only possible structure for the hydrazones.

The hydrazones, when treated with Fehling's solution, evolve no nitrogen, whereas, as we have seen, hydrazines evolve all their nitrogen under these conditions. This fact may be made use of to determine the carbonyl group quantitatively. A known weight of phenyl-hydrazine, in excess of that required, is added to the carbonyl compound, and the excess determined by measuring the nitrogen evolved on treatment with Fehling's solution.

On warming with acids the hydrazones are broken up back again to a greater or less extent, but seldom quantitatively, into ketone or aldehyde and phenyl-hydrazine. The best way of obtaining a carbonyl compound from a hydrazone, which is sometimes important when it is used for a separation, is to treat it with an aqueous solution of pyroracemic acid, when the hydrazone group migrates from the one compound to the other :—

$$\begin{matrix}R\\R_1\end{matrix}\!\!>\!C{=}N{-}NH\phi + CH_3CO{\cdot}COOH = \begin{matrix}R\\R_1\end{matrix}\!\!>\!C{=}O + CH_3C\!<\!\begin{matrix}N{-}NH\phi\\COOH\end{matrix}.$$

[1] *C.* **03.** i. 1129 ; ii. 491.

The hydrazones of fatty (not aromatic) carbonyl compounds add on hydrocyanic acid to give hydrazido-nitriles:—

$$\begin{matrix}\phi\cdot NH{-}N{=}CH\cdot CH_3\\ +\quad H\cdot CN\end{matrix} = \phi\cdot NH{-}NH\cdot\underset{\displaystyle CN}{\underset{|}{C}}H\cdot CH_3 .$$

By careful reduction they can sometimes be converted into hydrazido-compounds[1]:—

$$\phi\cdot NH{-}N{=}CH\cdot COOH \longrightarrow \phi\cdot NH{-}NH\cdot CH_2\cdot COOH.$$

Stronger reducing agents convert them at once into a mixture of amines:—

$$(CH_3)_2C{=}N\cdot NH\cdot\phi + 4\,H = (CH_3)_2CH\cdot NH_2 + NH_2\phi.$$

This is Tafel's method of preparing amines. The reducing agent used is either sodium amalgam and acetic acid in alcoholic solution, or, more recently, electrolysis in sulphuric acid.[2]

Gentle oxidation with amyl nitrite converts the phenyl-hydrazones into hydrotetrazones: e. g.

$$2\,\phi\cdot CH{=}N{-}NH\phi \longrightarrow \begin{matrix}\phi\cdot CH{=}N & N{=}CH\cdot\phi\\ \quad|\\ \phi\cdot N{-}N\cdot\phi\end{matrix}.$$

These bodies give a brilliant red solution in sulphuric acid. This is probably the origin of the Bülow reaction, a bright red or yellow colour which all hydrazones give when treated with a crystal of ferric chloride or potassium bichromate in concentrated sulphuric acid.

When they are heated with zinc chloride they give off ammonia, with the production of indol derivatives, a reaction which has not yet been satisfactorily explained:—

$$\phi\cdot NH{-}N{=}C\begin{matrix}CH_3\\ CH_3\end{matrix} \longrightarrow \begin{matrix}CH\\ NH\end{matrix}\!\!>\!C\cdot CH_3 .$$

$$\phi\cdot NH{-}N{=}CH\cdot CH_2\cdot CH_3 \longrightarrow \begin{matrix}C\cdot CH_3\\ \|\\ CH\\ NH\end{matrix} .$$

A large number of phenyl-hydrazones have been found to occur in two more or less stable modifications.[3] In all these cases the bodies are of the type $Ar\cdot NH{-}N{=}CRR_1$, while no such isomerism is observed in the derivatives of symmetrical ketones of the type $Ar\cdot NH{-}N{=}CR_2$. It is therefore probable that the two forms are stereoisomers, corresponding to the stereoisomeric oximes:—

$$\begin{matrix}R\cdot C\cdot R_1\\ \|\\ HO\cdot N\end{matrix}\quad,\quad\begin{matrix}R\cdot C\cdot R_1\\ \|\\ N\cdot OH\end{matrix}\quad:\quad\begin{matrix}R\cdot C\cdot R_1\\ \|\\ Ar\cdot NH{-}N\end{matrix}\quad,\quad\begin{matrix}R\cdot C\cdot R_1\\ \|\\ N{-}NH\cdot Ar\end{matrix}.$$

The other possible isomeric formula, that of the azo-compounds, $ArN{=}N\cdot CHRR_1$, is excluded by the fact that in many cases these bodies are known as well as the two forms of the hydrazone, and that they are coloured.

In the case of the derivative of cyanacetic ester, $Ar\cdot NH{-}N{=}C\begin{matrix}CN\\ COOR\end{matrix}$, Hantzsch and Thompson[4] find that in the α-modification the hydrogen attached to the nitrogen is more acidic than in the β-, and more easily replaced by the

[1] Cf. Schlenk, *J. pr. Ch.* [2] **78.** 49 (1908).
[2] Tafel, Pfeffermann, *C.* **02.** i. 1207. Cf. *Ber.* **33.** 2209 (1900).
[3] Cf. Lockemann, Liesche, *Ann.* **342.** 14 (1905).
[4] *Ber.* **38.** 2266 (1905).

acetyl group. They hence assume that in the α- this hydrogen is nearer to the acidifying CN group than in the other:—

$$\alpha\ \begin{matrix} NC\cdot C\cdot COOR \\ \| \\ Ar\cdot NH\text{–}N \end{matrix} \quad : \quad \beta\ \begin{matrix} NC\cdot C\cdot COOR \\ \| \\ N\text{–}NH\cdot Ar \end{matrix}.$$

This explanation is ingenious and probable; but it is to be noticed that the assumption is made here for the first time that the chemical influence of one group on another (as distinguished from the reaction of one group with another) is determined by their stereo-chemical distance apart.

The hydrazone of acetaldehyde, $\phi\cdot NH\text{–}N{=}C\begin{matrix} H \\ CH_3 \end{matrix}$, occurs in two forms,[1] melting at 98° and 57° respectively. Here the azo-compound, $\phi\cdot N{=}N\cdot CH_2\cdot CH_3$, is known, and is quite distinct. The isomerism of the hydrazones, as described, cannot be reconciled with any theory; for each is supposed to be the stable form, and one passes over into the other when treated with a trace of ammonia, while in presence of a trace of sulphur dioxide the reverse change takes place. It is evident that the two differ but little in stability, and that they are near their transition point, but the facts require further investigation.

Acetaldehyde-phenyl-hydrazone is formed from the isomeric ethane-azo-benzene by the action of strong acids[2]; and there is some reason to think that alkalies effect the reverse change. The azo-compound is red; and it has been suggested[3] that the red colour which many hydrazones assume on standing, and especially on exposure to light, is due to the change into the azo-compound. The ultra-violet absorption of the product supports this view.[4]

Para-nitro-phenyl-hydrazine[5] combines with acetone with such readiness, giving an almost insoluble hydrazone, that it can be used for the quantitative determination of acetone in methylated spirit, the spirit being treated with the hydrazine in acetic acid solution, and the precipitate filtered off and weighed.

The compound obtained from acetoacetic ester and phenyl-hydrazine is not a true hydrazone but a derivative of the enolic form of the ester. It must be phenyl-hydrazo-crotonic ester, since on oxidation it gives benzene-azo-crotonic ester. When warmed in vacuo to 200° it loses alcohol and forms phenyl-methyl-pyrazolone:—

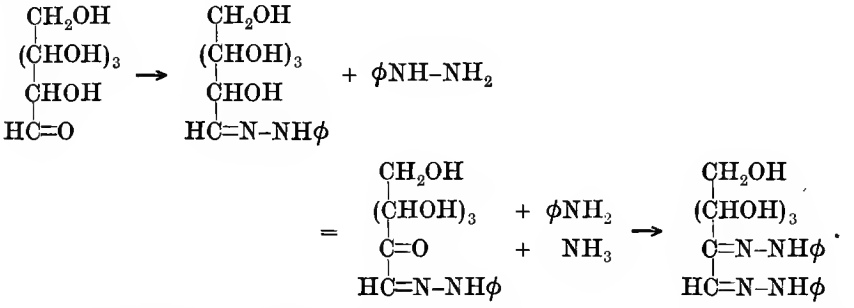
$$\begin{matrix} CH_3 \\ | \\ C\cdot N{=}N\cdot\phi \\ \| \\ CH \\ | \\ COOEt \end{matrix} \longleftarrow \begin{matrix} CH_3 \\ | \\ C\cdot NH\text{–}NH\phi \\ \| \\ CH \\ | \\ COOEt \end{matrix} \longrightarrow \begin{matrix} CH_3 \\ | \\ C\text{—}NH^* \\ | \quad > N\cdot\phi \\ HC\text{—}CO \end{matrix}$$

If the pyrazolone is treated with methyl iodide, the hydrogen atom marked with a * is replaced by methyl, giving dimethyl-phenyl-pyrazolone, which is antipyrine. This is the method used for the commercial preparation of this substance.

Compounds containing two carbonyl groups in the molecule can give both mono- and di-hydrazones. α-dihydrazones are known as osazones. These bodies are of great importance in the chemistry of the sugars, and are there formed by a peculiar reaction. The sugars have a hydroxyl group attached to every carbon

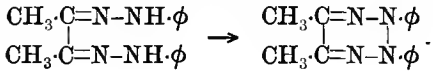
[1] Lockemann, Liesche, *Ann.* **342**. 14 (1905).
[2] E. Fischer, *Ber.* **29**. 793 (1896).
[3] Chattaway, *J. C. S.* **1906**. 462.
[4] Baly, Tuck, *J. C. S.* **1906**. 982.
[5] Blanksma, van Ekenstein, *Rec. Trav.* **22**. 434 (*C.* **04**. i. 14).

atom but one, that one having a carbonyl group in the form of ketone or aldehyde. On treatment with phenyl-hydrazine the carbonyl forms a hydrazone in the normal manner. But if excess of phenyl-hydrazine is used and the mixture warmed in acetic acid solution, the reaction goes further. Another molecule of the hydrazine removes two hydrogen atoms from the next CHOH, converting it into CO, which condenses with a third molecule, while the hydrogen removed reduces the phenyl-hydrazine into aniline and ammonia. For example:—

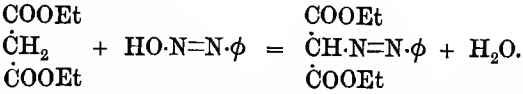


The corresponding ketose, $CH_2OH{\cdot}(CHOH)_3{\cdot}CO{\cdot}CH_2OH$, gives the same osazone. The importance of these osazones in the chemistry of the sugars is due to the fact that they are almost insoluble in water, whereas the hydrazones are very soluble. They can therefore be easily separated and identified by means of their melting-points, &c., whereas the sugars themselves are often difficult to crystallize, and so can neither be purified nor identified directly.

Many osazones, when treated with ferric chloride in alcoholic solution, give a red colour, by which they can be distinguished. This is due to their oxidation to osotetrazones:—



Besides the usual method of forming hydrazones—by the action of a carbonyl compound on phenyl-hydrazine—there is another which is commonly assumed to lead to the production of hydrazones (though this is not certain), and which is in any case of great theoretical interest. This consists in the action of diazo-compounds on open-chain bodies containing an acidic methylene group: that is, a CH_2 attached to negative groups such as NO_2, CO, or COOEt. Thus the primary nitroparaffins, β-keto-esters, malonic ester, &c., combine with diazo-bodies to form derivatives which were at first supposed by their discoverer, V. Meyer, to be azo-compounds:—



But V. Meyer found that this compound gave on saponification an acid identical with that obtained from mesoxalic acid and phenyl-hydrazine, which one would assume to be a hydrazone:—

$$\begin{matrix}\text{COOH}\\ \dot{\text{C}}{=}\text{O}\\ \dot{\text{C}}\text{OOH}\end{matrix} + \text{H}_2\text{N–NH}\phi = \begin{matrix}\text{COOH}\\ \dot{\text{C}}{=}\text{N–NH}\phi\\ \dot{\text{C}}\text{OOH}\end{matrix} + \text{H}_2\text{O}.$$

It was therefore evident that in one or other of these reactions an intramolecular change occurred. The question of the structure of these bodies was for a long time disputed. It is certainly a strong argument in favour of the azo-formula that they are all brightly coloured, as are all azo-compounds but no hydrazones. On the other hand, if the acetoacetic ester derivative, for example, is an azo-body,

$$\phi\text{·N=N·}\begin{matrix}\text{CO·CH}_3\\ \dot{\text{C}}\text{H}\\ \dot{\text{C}}\text{OOEt}\end{matrix},$$

an analogous compound,

$$\phi\text{·N=N·}\begin{matrix}\text{CO·CH}_3\\ \dot{\text{C}}\text{·CH}_3\\ \dot{\text{C}}\text{OOEt}\end{matrix},$$

should be formed from methyl-acetoacetic ester. But as a fact methyl-acetoacetic ester reacts with diazobenzene in quite a different way. The acetyl group splits off and the phenyl-hydrazone of pyroracemic acid, $\phi\text{·NH–N=C}\langle\begin{matrix}\text{CH}_3\\ \text{COOEt}\end{matrix}$, is produced.

The breaking of the carbon chain is most easily explained if we suppose that the divalent hydrazo-residue has to make a place for itself on the carbon by turning out not only the hydrogen but also the acetyl. It will be shown, however, that in bodies of this type the acyl groups have unusual mobility. It has been advanced in favour of the hydrazone structure that these bodies give the Bülow reaction for hydrazones; but in strong sulphuric acid, which is used in this reaction, tautomeric change is obviously probable.

The mechanism of these reactions, and the nature of the products, have been elucidated by Dimroth. The bodies which react with diazobenzene in this way are all such as exhibit keto-enolic tautomerism. Dimroth[1] selected cases (such as his own triazol derivatives, Claisen's mesityl-oxide-oxalic ester and triacyl-methanes, and Knorr's diaceto-succinic ester) where the two tautomers can be separated, and where it is known that under the conditions of the reaction one tautomer does not go over into the other; and he showed that in every instance the enol form reacts with diazobenzene and the ketone does not, and further that the enol reacts even in bodies of the type $\begin{matrix}\text{R}\\ \text{R}\end{matrix}\rangle\text{C=C}\langle\begin{matrix}\text{OH}\\ \text{R}\end{matrix}$, where there is no hydrogen attached to the carbon next to the COH group. The combination with the diazo-compound may thus take place in either of two ways:—

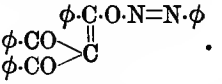
(1) $\begin{matrix}\text{–C·OH}\\ \|\\ \text{–C–}\end{matrix} + \text{HON=N·R} \rightarrow \begin{matrix}\text{–C}\langle\begin{matrix}\text{OH}\\ \text{OH}\end{matrix}\\ |\\ \text{–C–N=N·R}\end{matrix} \rightarrow \begin{matrix}\text{–C=O}\\ |\\ \text{–C–N=N·R}\end{matrix};$

(2) $\begin{matrix}\text{–C·OH}\\ \|\\ \text{–C}\\ |\end{matrix} + \text{HON=N·R} \rightarrow \begin{matrix}\text{–C·O·N=N·R}\\ \|\\ \text{–C}\\ |\end{matrix} \rightarrow \begin{matrix}\text{–C=O}\\ |\\ \text{–C–N=N·R}\\ |\end{matrix}.$

Further investigation[2] showed that the reaction takes the second course. For example, we may take the case of tribenzoyl-methane. The keto-form of

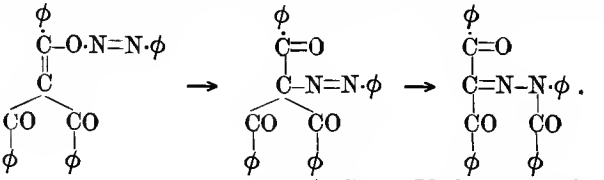
[1] *Ber.* **40.** 2404, 4460 (1907). [2] Dimroth, Hartmann, *Ber.* **41.** 4012 (1908).

this will not react. The enol form reacts easily, forming a yellow body, which should be an O-azo-compound with the structure



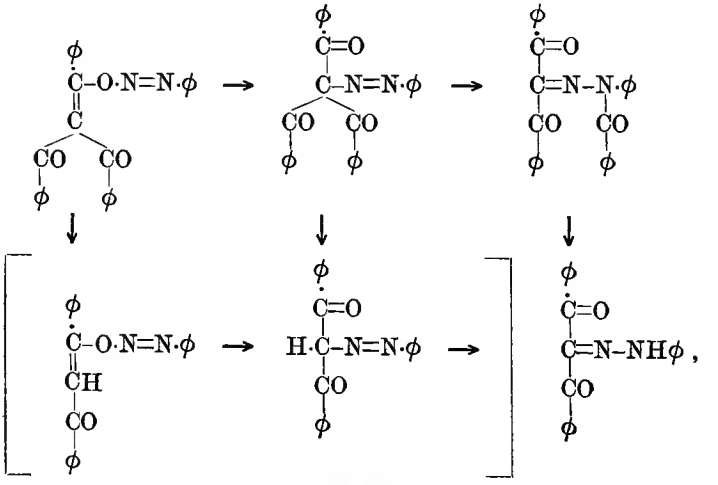
For if it is boiled with alcohol it breaks up into tribenzoyl-methane, nitrogen, and benzene, while the alcohol is oxidized to aldehyde. This is the behaviour of a diazo-ether, as are also its other properties: it couples with α-naphthol, it gives a diazonium salt with hydrochloric acid, and it reduces to phenyl-hydrazine, in all cases with regeneration of tribenzoyl-methane. It should, however, be noticed[1] that all these reactions only show that the body is not a C-azo-compound: they do not prove it to be an O-azo-compound. They are quite compatible with its being a diazonium salt,  .

If the dry substance is heated, it first turns red, and then colourless. The red substance is unstable, but can be isolated. It must be an N-azo-derivative; the N_2 group is firmly attached, and the body will neither couple with naphthol nor form a diazonium salt with hydrochloric acid. On reduction it gives a leuco-compound, which is the corresponding hydrazo-body. The white substance, made by heating the red or by acting on it with acid, is a hydrazone, and on reduction gives benzanilide. The whole reaction is therefore:—



Azo- (red). Hydrazone (colourless).

On treatment with sodium ethylate all these three compounds split off benzoic acid and form the phenyl-hydrazone of diphenyl-triketone. We may suppose that the reaction takes place thus:—



[1] Cf. Auwers, *Ber.* **41**. 4304 (1908).

the analogous series of changes taking place after the loss of one benzoyl group, with the difference that the reactions which require a measurable time in the former instance now occur instantaneously.

If we start with dibenzoyl-methane, we must suppose that the lower series of compounds are formed, and that the only product which can be isolated is the hydrazone.

These experiments show that as far as the acylated compounds are concerned, the hydrazone is the stable form. All attempts to convert the hydrazone back into the azo-body were unsuccessful. We may, therefore, fairly assume that in those compounds which have a hydrogen atom instead of the acyl group the hydrazone is still the stable form, and that the only difference will be that in this case the change will be more rapid. Hence the compounds formed by the action of diazo-bodies on substances with an acidic methylene group must be regarded as hydrazones.

This result, which seems beyond dispute, is particularly remarkable in view of the fact that, as we shall see later, in the aromatic series (oxyazo-compounds) the reverse is the case, and the stable form is the azo.

The readiness with which azo-compounds and hydrazones go over into one another (of which we have already had an example in ethane-azo-benzene and acetaldehyde-phenyl-hydrazone) is shown in the derivatives obtained from diazo-benzene and triacyl-methane.[1] If they are allowed to stand in indifferent solvents or heated above their melting-points, they lose their colour and pass, with the migration of an acyl group, into substances which are undoubtedly acyl-hydrazones:—

$$\phi\cdot N{=}N\cdot C(CO\cdot CH_3)_3 \rightarrow CH_3\cdot C\overset{\phi}{O}{>}N\text{–}N{=}C(CO\cdot CH_3)_2.$$

This mobility of the acyl group weakens the argument from the behaviour of methyl-acetoacetic acid.

The formulation of these bodies as hydrazones brings out the resemblance which exists between hydroxylamine and phenyl-hydrazine on the one hand, and nitrous acid and diazobenzene on the other. We have seen that there are two ways of making oximes: the normal method, by the action of hydroxyl-amine on a compound containing a carbonyl group:—

$$>C{=}O + H_2NOH = >C{=}NOH + H_2O,$$

and a second method, by the action of nitrous acid on bodies containing an acidic methylene:—

$$>C{=}H_2 + O{=}NOH = >C{=}NOH + H_2O.$$

The two are so to speak reciprocal; in the first the doubly linked oxygen is on the carbon and the H_2 on the nitrogen; in the second the oxygen is attached to nitrogen and the hydrogen to carbon.

Exactly the same relations hold in the case of the hydrazones, which differ from the oximes only in having the OH of the :NOH replaced by $NH\phi$. Corresponding to the normal formation of oximes from ketone and hydroxylamine is the formation of hydrazones from ketone and phenyl-hydrazine:—

$$>C{=}O + H_2N\text{–}NH\phi = >C{=}N\text{–}NH\phi + H_2O,$$

[1] Dimroth, Hartmann, *Ber.* **40**. 4460 (1907).

and corresponding to the action of nitrous acid on the methylene group that of diazobenzene, which also only occurs when this group has acidic properties, and which may be written :—

$$>CH_2 + O{:}N{-}NH\phi = >C{:}N{-}NH\phi + H_2O,$$

so as to bring out the analogy. A further point of resemblance is that in both classes of reactions—with nitrous acid and with diazobenzene—we get under similar conditions a breakage of the carbon chain, as is shown in the acetoacetic ester group :—

With acetoacetic ester:

$$\begin{array}{lcl} CH_3{\cdot}C{=}O & CH_3{\cdot}C{=}O & CH_3{\cdot}C{=}O \\ \dot{C}{=}NOH & \dot{C}H_2 & \dot{C}{=}N{-}NH\phi\,. \\ \dot{C}OOEt & \dot{C}OOEt & \dot{C}OOEt \end{array}$$

With acetoacetic acid:

$$\begin{array}{lcl} CH_3{\cdot}C{=}O & CH_3{\cdot}C{=}O & CH_3{\cdot}C{=}O \\ H{\cdot}\dot{C}{=}NOH & \dot{C}H_2 & H{\cdot}\dot{C}{=}N{-}NH\phi\,. \\ +\ CO_2 & \dot{C}OOH & +\ CO_2 \end{array}$$

With methyl-acetoacetic ester:

$$\begin{array}{lcl} CH_3{\cdot}COOH & CH_3{\cdot}C{=}O & CH_3{\cdot}COOH \\ CH_3{\cdot}C{=}NOH & CH_3{\cdot}\dot{C}{\cdot}H & CH_3{\cdot}C{=}N{-}NH\phi\,. \\ \dot{C}OOEt & \dot{C}OOEt & \dot{C}OOEt \end{array}$$

HYDRAZO-COMPOUNDS

The hydrazo-compounds are those hydrazine derivatives in which one hydrogen of each NH_2 is replaced by an aromatic radical. Their behaviour differs in many respects from that of the other hydrazine derivatives.

They were discovered by Hofmann in 1863. They are obtained by the reduction of the nitro-compounds in alkaline solution, for example by the action of zinc dust, or by electrolysis. A remarkable method of forming them is by the action of chloro-dinitro- or chloro-trinitro-benzene (in which the chlorine is mobile) on phenyl-hydrazine :—

$$(NO_2)_2C_6H_3{\cdot}Cl + H_2N{-}NH\phi = (NO_2)_2C_6H_3{\cdot}NH{-}NH\phi + HCl.$$

They are colourless crystalline substances, and are in fact the leuco-compounds of the azo-series. They are soluble in alcohol, but not in water. They become coloured in air, especially in the presence of moisture, and still more in that of alkali, going over partially into the azo-compounds. They are neither basic nor acidic, the amino-group being neutralized by the negative phenyl.

On energetic reduction they give two molecules of amine. In many cases this occurs with especial ease at the moment of their formation, so that it is often difficult to stop the reduction of the azo-compounds at the right point.

The hydrazo-compounds cannot be distilled, as on heating one molecule gives up its two hydrogen atoms to another, forming the azo-derivative and two molecules of amine :—

$$2\ \phi NH{-}NH\phi = \phi{-}N{=}N{-}\phi + 2\ \phi NH_2.$$

The hydrogen attached to the nitrogen is easily replaced, acetic anhydride,

for example, forming a di-acetyl derivative, phenyl isocyanate a urea, and nitrous acid at low temperatures a very unstable yellow crystalline compound, which probably has the formula $\begin{matrix}\phi\cdot N & --- & N\cdot\phi \\ | & & | \\ NO & & NO\end{matrix}$.

The most remarkable reaction of the hydrazo-compounds is their intramolecular change to benzidine and similar bodies. This occurs with great ease on treatment with acids, so that if azobenzene is reduced in acid solution the hydrazo is not obtained at all, but only the products of its rearrangement. The reaction has already been sufficiently discussed. It is enough to repeat that it goes in two stages, giving first a semidine (*p*-amino-diphenyl-amine) and then a diphenyl derivative, either benzidine (di-*p*-diamino-diphenyl) or, if the para position is occupied, a diphenyline, which is the corresponding ortho-para-diamino-compound.

Hydrazo-triphenyl-methane, $\phi_3C\cdot NH\text{–}NH\cdot C\phi_3$, like so many other compounds containing this radical, has a very peculiar behaviour.[1] It is a comparatively stable substance, and is not oxidized at all by the air, or by silver oxide. Stronger oxidizing agents, such as potassium permanganate or chromic acid, remove the hydrogen of the hydrazo-group, but the azo-compound, $\phi_3C\cdot N{=}N\cdot C\phi_3$, which we must suppose to be found, at once breaks up into nitrogen and triphenyl-methyl, ϕ_3C, which appears as its peroxide, $\phi_3C\cdot O\cdot O\cdot C\phi_3$.

Thus the relations which hold with the simple aromatic derivatives (such as hydrazobenzene) are here reversed. The hydrazo-compound is much more stable, and the azo-body almost infinitely less so. Wieland expresses this by saying that the weak affinity of the triphenyl-methyl group makes the attachment of the hydrogen to the nitrogen in the hydrazo-compound much weaker than in hydrazobenzene, while it is unable to hold the azo-group at all.

[1] Wieland, *Ber.* **42.** 1902 (1909).

CHAPTER XI

DIAZO-COMPOUNDS[1]

THE next group of compounds consists of the derivatives of the hypothetical diimide HN=NH. Here, as in the hydrazine compounds, we have to distinguish two classes of bodies: those in which one of the two nitrogen atoms is attached to a hydrocarbon group, and those in which both are so attached. The difference here is, however, for whatever reason, far more striking than among the hydrazines.

The diazo-compounds are those in which the N_2 group is attached only on one side to a hydrocarbon radical.

It is to be noticed that the so-called fatty diazo-compounds do not belong to this group, since they have the N_2 joined at both ends to the same carbon atom, as in diazo-methane, $CH_2\begin{matrix}N\\ \|\\ N\end{matrix}$. They will therefore be discussed among the ring compounds. The very small number of true diazo-compounds of the fatty series which are known are more conveniently dealt with along with the diazomethane derivatives.

The study of the diazo-compounds has contributed to the development of organic chemistry in an extraordinary degree and in a variety of ways. The detection and isolation of bodies of so unstable and explosive a nature required the highest experimental skill. The compounds were of the utmost service to synthetical chemistry, owing to the great variety of groups which they made it possible to introduce into the benzene nucleus; they are of immense technical importance as the foundation of the vast group of azo-dyes; and in recent times the study of their constitution has thrown great light on some of the obscurest questions of tautomeric change.

The diazo-compounds were discovered by Peter Griess[2] in 1858. Their importance for synthetic and technical purposes was soon realized, and their more important reactions were established. Then, more than thirty years later, the question of their constitution, which seemed to have been fairly satisfactorily settled, was again raised, and became the subject of a prolonged controversy between Hantzsch and Bamberger, in which both sides exhibited the highest degree of skill, and Hantzsch in particular developed a new and most fruitful method—the electrochemical—of attacking problems of this kind. The controversy has finally been decided in Hantzsch's favour. It is clear that we

[1] Cf. Hantzsch, *Die Diazoverbindungen*, Sammlung Ahrens, Bd. viii (Enke, Stuttgart, 1903); Eibner, *Zur Geschichte der aromatischen Diazoverbindungen* (Oldenbourg, Munich, 1903); Cain, *Chemistry of the diazo-compounds* (Arnold, 1908). See also Morgan, *Brit. Ass. Reports*, **1902**, p. 181, and *Ch. News*, **86**. 189, 204, 213, 225 (1902).

[2] *Ann.* **106**. 123.

have to deal with an extremely complicated case of combined tautomerism and stereoisomerism, the diazo-group being capable of assuming no less than four different configurations. By his elucidation of these extraordinarily intricate relationships Hantzsch has won a place in the first rank of chemists, and has advanced our knowledge of the intimate nature of chemical reactions to a remarkable degree.

Before discussing these questions, it will be well to consider briefly the methods of formation and the more important reactions of the diazo-compounds. In order not to prejudge the question of constitution, this will be represented by the symbol N_2.

Methods of formation

1. By the action of nitrous acid on primary aromatic amines: either

(*a*) By passing the gaseous oxides of nitrogen evolved from starch or arsenic trioxide and nitric acid into a solution of the amine salt. This is the usual method for isolating the solid diazo-salts in the laboratory, and was the way in which Griess originally prepared them. The gas is passed into a paste of the amine salt and a little water, cooled with ice. The much more soluble diazo-salt goes into solution, and is precipitated with alcohol and ether. A modification[1] of this method is to diazotize the sulphuric acid solution with barium nitrite (which can now be easily obtained), to filter off the barium sulphate, and to add a mixture of alcohol and ether to the filtrate.

(*b*) By the action of alkyl (ethyl or amyl) nitrite on an acid solution of the amine.[2] This depends on the extraordinary rapidity with which the alkyl nitrites break up in the presence of acid. It is sometimes used to make the solid diazo-salt; the amine salt is dissolved in alcohol, and the alkyl nitrite added. An almost quantitative yield of the solid diazo-salt may be got by dissolving or suspending the amine salt in glacial acetic acid, cooling below 10°, adding a slight excess of amyl nitrite, and precipitating with ether.[3]

(*c*) By the action of nascent nitrous acid on the amine salt, i. e. by adding sodium nitrite to the acid solution. This is by far the commonest method when, as is usually the case, an aqueous solution only is wanted, and the precautions necessary in preparing the solid salt (which are due to its great solubility in water and its insolubility in ether, making it impossible to separate it from a soluble inorganic salt) are no longer required. But other precautions have to be observed. It is important to use the exact equivalent of sodium nitrite, and allowance must be made for the impurity which this salt always contains. The nitrite solution may be titrated, or as a rough guide the salt assumed to contain 98 per cent. of nitrite; the older books recommended taking the molecular weight of sodium nitrite as 72 instead of 69, but it is now generally better than this. A common way is to run in the nitrite solution until the liquid will darken starch-potassium iodide paper, showing the presence of free nitrous acid.

The amount of acid used is also an important factor. Theory requires two

[1] Witt, Ludwig, *Ber.* **36**. 4384 (1903). [2] Knoevenagel, *Ber.* **23**. 2995 (1899).
[3] Hantzsch, Jochem, *Ber.* **34**. 3337 (1901).

molecules of hydrochloric acid to one NH_2. Generally more than this must be used: commonly two and a half molecules, but in exceptional cases a still larger excess.

The temperature must be carefully regulated. The ordinary rule is to cool the amine solution beforehand to 5° or below, and not to allow it to rise above 10° during the reaction. It is then still kept cold, and used within twenty minutes. But with some amines the diazotization goes slowly, and it is necessary to work at the ordinary temperature, or even slightly above it.

If the amine salt is only sparingly soluble in water it can be suspended in a state of fine division, as the diazo-salt is always much more soluble. When the amine is so feebly basic that its salt is broken up by water, it is sometimes suspended in the sodium nitrite solution and the acid run in; or the base may be dissolved in strong nitric acid, and the nitrous acid formed in the solution by adding potassium pyrosulphite, $K_2S_2O_5$, which reduces some of the nitric acid: potassium nitrite cannot be used in this case, as it reacts too violently with the strong acid.[1]

Under ordinary conditions the diazotization of a base by nitrous acid takes place with great rapidity. But Hantzsch and Schümann[2] have been able, by using very dilute solutions, to measure its velocity. They determined the extent to which the reaction had proceeded by measuring the amount of undecomposed nitrous acid remaining by means of the colour which it gave with zinc iodide and starch. They showed that all amines examined (both positively and negatively substituted anilines) were diazotized with the same velocity; that this velocity was proportional to the product of the concentrations of the nitrous acid and the base; that it was somewhat increased by an excess of hydrochloric acid, but that a greater excess than one equivalent of acid had no further effect. This indicates that the reaction takes place between the undissociated nitrous acid and the cation of the base. In the presence of hydrochloric acid the nitrous acid, being a weak acid (about twice as strong as formic acid), will be practically undissociated; and the increase of velocity in presence of excess of acid must be due to the disappearance of the hydrolysis of the aniline salt, and the consequent increase of its cations. Similar results were obtained by Schümann,[3] by determining the velocity from the fall of conductivity of the solution.

Other methods for preparing the diazo-compounds are:

2. In some cases by treating the amine with another diazo-compound. Thus nitro-diazobenzene and toluidine give nitraniline and diazotoluene.

3. By the oxidation of aryl-hydrazines with mercuric oxide.

4. By the action of a diazonium perbromide on an aryl-hydrazine:—

$$2\ Ar{\cdot}N_2{\cdot}Br_3 + Ar{\cdot}N_2H_3 = 3\ Ar{\cdot}N_2Br + 3\ HBr.$$

This affords a convenient method for preparing the solid diazonium salt. The perbromide is suspended in alcohol, an alcoholic solution of the hydrazine added, and the precipitation completed with ether.[4]

5. By the reduction of the amine nitrate with zinc and hydrochloric acid. This is really a modification of 1.

[1] Witt, *Ber.* **42**. 2953 (1909).
[2] *Ber.* **32**. 1691 (1899).
[3] *Ber.* **33**. 527 (1900).
[4] Chattaway, *J. C. S.* **1908**. 958.

6. By the action of hydroxylamine on a nitroso-derivative:—

$$Ar{\cdot}NO + H_2N{\cdot}OH = Ar{\cdot}N_2{\cdot}OH + H_2O.$$

In this reaction the normal[1] and not, as was previously supposed,[2] the iso-diazotate is formed. The importance of this result will be seen later.

7. A peculiar method[3] is by treating certain nitroso-compounds with nitrous acid, some of which is oxidized to nitric acid:—

$$Ar{\cdot}NO + 3\,HNO_2 = Ar{\cdot}N_2{\cdot}ONO_2 + HNO_3 + H_2O.$$

Properties

As the diazo-compounds do not, as a rule, require to be isolated, there is comparatively little known about their individual properties, considering that almost every primary aromatic amine which has been described has been diazotized. But thanks to the work of Griess, and especially, in more recent times, to that of Hantzsch and his pupils, we have considerable knowledge of some of the simpler derivatives.

The mineral acid salts of diazobenzene are colourless crystalline solids, very easily soluble in water, less in alcohol, and scarcely at all in ether. They have the full character of salts, being highly ionized and not hydrolysed, as is shown by their having, when pure, a neutral reaction. They are endothermic bodies,[4] and in the dry state explode when heated, and sometimes when struck. The nitrate in particular is violently explosive, far more so than nitrogen iodide or mercury fulminate; the sulphate much less so. If the aqueous solution is shaken with nitrobenzene, benzene, chloroform, &c., not a trace of the diazo-compound is taken up; but it can be easily and completely removed by phenol, which turns a deep brown, possibly from the formation of diazobenzene-phenyl ester, $\phi{\cdot}N_2O{\cdot}\phi$.[5] The aqueous solutions of diazo-salts are usually stable if they are kept cold; but on heating the diazo-nitrogen is evolved quantitatively and a phenol is produced.

The haloid salts have a characteristic power of taking up two more atoms of halogen to form perhalides, such as $\phi{\cdot}N_2{\cdot}Br_3$, which are analogous to the alkaline perhalides, like KI_3. They are crystalline feebly explosive compounds, which on treatment with ammonia give azides, e.g. $\phi{\cdot}N_3$.

The N_2 group, though normally a strong base, is also capable of behaving as a weak acid. If a concentrated aqueous solution of diazobenzene chloride is poured into a large excess of very concentrated potash, potassium benzene diazotate, ϕN_2OK, separates out. But this and similar bodies will be considered in dealing with the question of constitution.

The next reactions to be discussed are those in which the diazo-bodies pass into compounds of other types, and of these first those in which the diazo-nitrogen is eliminated. It is these reactions which have given the diazo-compounds their enormous importance for synthetical work. They all consist in the evolution of the whole of the nitrogen of the N_2 group as gas, while its place

[1] Hantzsch, *Ber.* **38.** 2056 (1905). [2] Bamberger, *Ber.* **28.** 1218 (1895).
[3] O. Fischer, Hepp, *Ann.* 255. 144 (1889); Hantzsch, *Ber.* **35.** 894 (1902).
[4] Berthelot, Vielle, *C. R.* **92.** 1076 (1881).
[5] Hirsch, *Ber.* **23.** 3705 (1890); Norris, Macintire, Corse, *Am. Ch. J.* **29.** 120 (1903).

on the ring is taken by some other radical present, commonly that which was previously attached to the diazo-group as an acid radical. There are scarcely any of the simpler groupings which cannot in this way be introduced into the ring under suitable conditions.

Thus we can replace the N_2 by the following groups:

1. Hydroxyl. This usually occurs very readily, on keeping or heating the aqueous solution of the diazo-salt. It is best to use the chloride or sulphate; if the nitrate is employed the phenol is liable to be attacked by the liberated nitric acid. In some cases it is not sufficient even to boil with water, but the salt must be heated with moderately concentrated sulphuric acid of boiling-point 140–150°, or with copper sulphate solution. The presence of a chlorine atom, or still more of a methoxy- or ethoxy-group in the ortho position to the diazo, greatly hinders this reaction.

2. Alkoxyl, with the formation of phenol ethers. This change often occurs readily on boiling with absolute alcohol, but the reaction in many cases goes in a different way, the diazo-group being replaced by

3. Hydrogen, with the production of the hydrocarbon, the alcohol being oxidized to aldehyde:—

$$\phi\cdot N_2\cdot Cl + CH_3\cdot CH_2OH = \phi\cdot H + HCl + N_2 + CH_3\cdot CHO.$$

Which of these two reactions takes place depends entirely on the precise conditions. Thus if diazobenzene-sulphonic acid[1] (with the sulphur on the nucleus) is treated with methyl alcohol under diminished pressure, only benzene-sulphonic acid is formed; but the same reagents under thirty atmospheres pressure give only anisol-sulphonic acid, $CH_3O\cdot C_6H_4\cdot SO_3H$; while at the ordinary pressure a mixture of the two is obtained. The formation of phenol ethers is, however, the normal reaction. The presence of negative groups, especially in the ortho position, promotes the replacement by hydrogen.[2]

The production of the hydrocarbon is often effected by treating the alcoholic solution or suspension of the amine salt with amyl nitrite, and then boiling.

The diazo-group can also be replaced by hydrogen in other ways. The body can be reduced to the hydrazine, and then this converted into the hydrocarbon by oxidation with copper sulphate or ferric chloride as already described. Or the diazo-group may be replaced by iodine, and the product reduced, for example, by distillation over zinc dust. A reaction which is often used for this purpose is Friedländer's. This consists in treating the diazo-salt with an alkaline stannous solution. It has been shown[3] that in this reaction part of the salt is reduced to the hydrazine, which is then oxidized by the rest of the diazo-compound to the hydrocarbon.

4. Halogens. This is effected in various ways: sometimes by heating with excess of hydrochloric or hydrobromic acid, or by heating the platinichloride with soda.

The best method is that of Sandmeyer,[4] which consists in heating the chloride or bromide in presence of cuprous chloride or bromide:—

$$Ar\cdot N_2\cdot Br = Ar\cdot Br + N_2.$$

[1] Remsen, Palmer, *Am. Ch. J.* **8**. 243 (1886); Remsen, Dashiell, ib. **15**. 105 (1893).
[2] Remsen, Palmer, l. c.; Cameron, ib. **20**. 229 (1898).
[3] Eibner, *Ber.* **36**. 813.
[4] *Ber.* **17**. 1633, 2650 (1884).

The diazo-solution is usually added to the cuprous solution, which has been warmed to a suitable temperature. Sometimes the amine is diazotized in presence of the cuprous salt. In many cases it is better to adopt Gattermann's modification,[1] and to treat the diazo-solution with copper powder, which decomposes it in the cold. The powder is prepared by adding zinc dust through a fine sieve to a cold saturated copper sulphate solution, and then washing the precipitated copper with water and hydrochloric acid.

Iodine requires none of these elaborations. It is enough to pour the diazonium sulphate solution into potassium iodide solution, or vice versa.

In order to replace the diazo-group by fluorine the diazo-salt is coupled with piperidine to form the diazo-piperidide

$$Ar{\cdot}N{=}N{\cdot}N\langle\begin{matrix}CH_2{-}CH_2\\CH_2{-}CH_2\end{matrix}\rangle CH_2,$$

and when concentrated hydrofluoric acid is poured over this it breaks up into fluorbenzene, nitrogen, and piperidine hydrofluoride:—

$$\phi{\cdot}N{=}N{\cdot}NC_5H_{10} + 2\,HF = \phi{\cdot}F + C_5H_{11}N{\cdot}HF + N_2.$$

5. Cyanogen. This is a most important discovery of Sandmeyer's, enabling us to introduce the carboxyl group into an aromatic compound. The diazo-solution is poured into a hot solution of potassium cuprous cyanide, made by the action of potassium cyanide on copper sulphate.

6. Various groups containing sulphur may be introduced by decomposing the diazo-salt with potassium xanthogenate (potassium ethyl-dithiocarbonate $S{=}C\langle\begin{matrix}S{\cdot}K\\OEt\end{matrix}$). If they are heated alone they give carbon oxysulphide and the thio-ether Ar·S·Et; and if they are heated with alkali they give carbon oxysulphide, alcohol, and the thio-phenol Ar·SH.

7. The nitro-group. This replacement is not usually required; but it is useful in certain cases. For example, β-nitro-naphthalene cannot be obtained by direct nitration, whereas β-naphthylamine is easily got from β-naphthol. In order to introduce the nitro-group the diazo-solution is treated with an equivalent of sodium nitrite, and the diazonium nitrite so formed is decomposed by cuprous oxide.

8. Aromatic hydrocarbon groups, such as phenyl, can be introduced by acting on the dry diazo-salt with the requisite hydrocarbon: if necessary aluminium chloride can be used as a catalyst, or in other cases an acyl chloride such as acetyl chloride[2]:—

$$\phi{\cdot}N_2{\cdot}Cl + H{\cdot}\phi = \phi{\cdot}\phi + N_2 + HCl.$$

Again, if the brown solution obtained by extracting a diazo-solution with phenol is heated,[3] oxy-diphenyls are produced:—

$$\phi{\cdot}N_2{\cdot}Cl + H{\cdot}C_6H_4OH = \phi{\cdot}C_6H_4OH + N_2 + HCl.$$

This by no means exhausts the list of radicals which can be introduced in place of the diazo-group, but it includes all those of any considerable importance.

Of the diazo-reactions in which the N_2 group is not removed, some have

[1] *Ber.* **23**. 1218 (1890).

[2] See references in Meyer and Jacobson, *Lehrbuch*, ii. 2. 17.

[3] Norris, *C.* **03**. i. 705.

already been mentioned, such as the combination with certain methylene compounds to form hydrazones. There are also others of great importance. Thus on reduction the diazo-compounds give primary aryl-hydrazines:—

$$Ar{\cdot}N_2{\cdot}Cl + 4\,H = Ar{\cdot}NH{\cdot}NH_2 + HCl.$$

On oxidation in alkaline solution they give nitroso-compounds and then nitramines, such as diazobenzenic acid or phenyl nitramine, $\phi{\cdot}NH{\cdot}NO_2$.

The so-called coupling reactions are of immense technical importance. They take place in two ways:—

1. With amines (fatty or aromatic) the first product is a diazoamino-compound[1]:—

$$\phi{\cdot}N_2{\cdot}Cl + \phi{\cdot}NH_2 = \phi{\cdot}N{=}N{-}NH\phi + HCl.$$

2. Directly in some cases (e.g. with some tertiary aromatic amines[2]) and always easily by a rearrangement of the first product an aminoazo-compound is formed. This is the typical 'coupling', the N_2 group attaching itself to the nucleus to give an azo-derivative. Thus an amine gives an aminoazo-derivative:—

$$\phi{\cdot}N_2{\cdot}Cl + H\langle\rangle NH_2 = HCl + \phi{\cdot}N{=}N{-}\langle\rangle{-}NH_2;$$

and in the same way phenols form oxy-azo-compounds:—

$$\phi{\cdot}N_2{\cdot}Cl + H\langle\rangle OH = HCl + \phi{\cdot}N{=}N{-}\langle\rangle{-}NH_3.$$

These products will be further discussed under the azo-derivatives.

Constitution of the Diazo-compounds

The original formula proposed by Griess[3] for the diazo-compounds regarded them as derived from the hydrocarbons by the replacement of two atoms of hydrogen by two of nitrogen, whence the name diazo. The salts were supposed to be formed by the direct addition of acid: thus

$$\text{Diazobenzene } C_6H_4N_2 \;:\; \text{chloride } C_6H_4N_2{\cdot}HCl.$$

Kekulé[4] had no difficulty in overthrowing this view. He showed that in all reactions in which the diazo nitrogen is removed a mono-substitution product remains. Hence the diazo-salt must be written $Ar{\cdot}N_2{\cdot}Cl$. This he expanded into $Ar{\cdot}N{=}N{\cdot}Cl$ for the salt, and $Ar{\cdot}N{=}N{\cdot}OH$ for the free base.

In 1869 Blomstrand suggested another formula.[5] He argued that the diazo-salts were strictly analogous to the ammonium salts, and therefore must contain pentad nitrogen. Hence he wrote them $Ar{\cdot}N\langle\!\!\langle^{N}_{Cl}$, corresponding to $Ar{\cdot}N\langle\!\!\langle^{H_3}_{Cl}$. The same view was put forward independently and almost at the same time by Strecker,[6] but on a different ground—that the very unstable diazo-compounds were so unlike the comparatively very stable azo-bodies, which were undoubtedly $Ar{\cdot}N{=}N{\cdot}Ar$, that they could not be built up on the same type. Erlenmeyer[7] suggested the same structure, also independently, in 1874.

[1] For the occurrence of this reaction among the fatty amines see Dimroth, *Ber.* **38.** 2328 (1905), and among the benzylamine bases, Goldschmidt, Holm, *Ber.* **21.** 1016 (1888).

[2] Haeussermann, *Ber.* **39.** 2762 (1906).

[3] *Ann.* **121.** 257 (1862); **137.** 39. (1866).

[4] *Lehrb. d. org. Chem.*, ii. 717 (1866).

[5] *Chemie der Jetztzeit*, **4.** 272; *Ber.* **8.** 51 (1875).

[6] *Ber.* **4.** 786 (1871).

[7] *Ber.* **7.** 1110.

Blomstrand and Strecker's views were, however, little regarded, and Kekulé's formula was generally accepted, especially after Emil Fischer's work[1] on the hydrazines. Fischer showed that diazobenzene could easily be converted by reduction into phenyl-hydrazine, whose formula he proved to be $\phi\cdot NH\cdot NH_2$. This is to be expected from Kekulé's diazo-formula:—

$$\phi\cdot N{=}N\cdot OH + 4\,H \longrightarrow \phi\cdot NH\cdot NH_2,$$

while Blomstrand's formula (tautomerism being of course at this time excluded) required that the product should be $\phi\cdot NH_2{=}NH$.

The question remained in this position for over ten years. Much attention was bestowed upon the diazo-compounds, but it was devoted entirely to working out the practical details of the reactions in which the diazo-group was replaced by other groups, and it threw little or no light on the constitution of these bodies.

In 1892 the question of constitution was again raised by v. Pechmann.[2] On the formation of hydrazones by the interaction of diazo-salts with methylene compounds, and on the general similarity of behaviour of the diazo-compounds and nitrous acid, he based a new formula, that of a nitrosamine, Ar·NH·NO. This view received additional support from the discovery of v. Pechmann and Wohl[3] that diazobenzene reacts with benzoyl chloride to give nitrosobenzanilide, which is easily explained on the nitrosamine formula:—

$$\phi\cdot NH\cdot NO + Cl\cdot CO\cdot\phi = \begin{matrix}\phi\cdot N\cdot NO\\ |\\ CO\cdot\phi\end{matrix} + HCl,$$

but which on Kekulé's theory requires us to suppose an elaborate addition process.

Two years later (1894) the problem entered on a new stage with the discovery of isomers of the diazo-compounds, which was made simultaneously and independently by Schraube and Schmidt,[4] by v. Pechmann and Frobenius,[5] and by Bamberger.[6] They found that potassium diazobenzene possesses entirely the character of a diazo-compound, and in particular the power of coupling, for example with β-naphthol, to give an azo-dye. But if it is heated with its mother liquor (excess of concentrated potash) the precipitate no longer couples, although after treatment with excess of acid it will again do so. This new body was called the iso-diazo-salt, and as Schraube and Schmidt found that it reacted with methyl iodide to give nitroso-methyl-aniline, $\phi\cdot NCH_3\cdot NO$, they assumed that it had the structure $\phi\cdot NK\cdot NO$, derived from v. Pechmann's nitrosamine formula. In view of v. Pechmann's arguments for this structure, it is remarkable that the iso-diazo-compound will not give hydrazones with aceto-acetic ester and similar bodies. The argument from the reactions of the potassium salt is one of a class which we know are not to be trusted; and v. Pechmann showed its weakness by proving that the silver salt of iso-diazobenzene gave with methyl iodide the O-ether of normal diazobenzene, $\phi\cdot N{=}N\cdot OCH_3$.

All this work on the iso-diazo-compounds was done in 1894. In the same year Hantzsch[7] produced a paper in which he reviewed the whole question, and

[1] *Ber.* **8.** 589, 1005 (1875); **9.** 881 (1876). [2] *Ber.* **25.** 3505 (1892); **27.** 651 (1894).
[3] Wohl, *Ber.* **25.** 3631 (1892). [4] *Ber.* **27.** 514. [5] *Ber.* **27.** 672. [6] *Ber.* **27.** 679.
[7] *Ber.* **27.** 1702 (1894).

offered a novel solution. He pointed out that there was a remarkable analogy between the history of the diazo-compounds and that of the oximes. The explanation offered by Schraube and Schmidt of the isomerism of the former corresponded exactly to that which Beckmann had given of the isomeric oximes; and it was possible to give a stereo-chemical explanation of the isomerism of the diazo-compounds similar to that by which he and Werner had solved the oxime problem. There are three analogous series of compounds which all admit of the same stereoisomerism:—

R·C·H ‖ R·C·H	:	R·C·H ‖ N·OH	:	R·N ‖ N·OH .
Fumaric, maleic.		Oxime.		Diazo.

He further argued that the evidence offered in support of the nitrosamine formula for the diazo-compounds was worthless, and that the normal and iso-alkaline salts must have the same structural formula, and must therefore be stereoisomers. The more easily decomposed normal compounds were assumed to have the syn-formula, $\begin{matrix}\phi\cdot N\\ \|\\ X\cdot N\end{matrix}$, and the more stable iso-salts the anti-, $\begin{matrix}\phi\cdot N\\ \|\\ N\cdot X\end{matrix}$.

To sum up, the state of affairs in 1894, after the appearance of Hantzsch's paper, was this. Two different series of isomeric diazo-compounds were known, the normal and the iso; and there were four different formulae in the field:—

1. Kekulé's, Ar·N=N·OH (Diazo).
2. Blomstrand's, $Ar.N\overset{N}{\underset{OH}{\diagdown\!\!\diagup}}$ (Diazonium).
3. v. Pechmann's, Ar·NH·NO (Nitrosamine).
4. Hantzsch's stereoisomers of Kekulé's formula, $\begin{matrix}Ar\cdot N\\ \|\\ HO\cdot N\end{matrix}$ and $\begin{matrix}Ar\cdot N\\ \|\\ N\cdot OH\end{matrix}$ (Syn- and anti-diazo).

As will appear later, all these formulae are under some conditions correct.

It is not necessary to follow the historical development of the question any further, or to describe the long controversy which ensued between Hantzsch and Bamberger. Hantzsch modified his original views on several important points; but he has established his theory, with these modifications, on so firm an experimental basis, that we need not consider the rival theories which have been proposed. The views as to the constitution of the diazo-compounds which are now accepted are in all essentials those of Hantzsch, and their more important points are summarized in the following pages.

We will consider first the salts of the diazo-compounds with the mineral acids. Here the evidence is conclusive in favour of Blomstrand's pentad nitrogen formula, which Hantzsch has called the diazonium formula, to indicate its analogy to that of the ammonium salts:—

Ar·N≡N | X	H·N≡H$_3$ | X ,	Ar·N≡H$_3$ | X
Diazonium.	Ammonium.	

This was revived by Bamberger in 1895 in opposition to Hantzsch's stereochemical views; it was soon adopted by Hantzsch himself, to whom the most important arguments in its favour are due. These consist in an elaborate com-

parison of the chemical and physico-chemical properties of these salts with those of the corresponding salts of the alkalies and the quaternary ammonium bases.

In the first place, it is obvious that the diazo-salts do not behave like compounds of triad nitrogen. We have an example of triad nitrogen with a hydroxyl group attached in hydroxylamine $H_2N{\cdot}OH$. This is not only a very weak base, but when it forms salts with acids it does so by addition, giving, for example, a hydrochloride, $H_2NOH{\cdot}HCl$. The diazo-salts, on the other hand, are derived from a very strong base, which in some of the substituted compounds is far stronger than ammonia, and almost if not quite as strong as the alkalies. Also when it forms salts it does not do so by addition, but by replacing the hydroxyl by an acid radical. In both of these points it closely resembles a quaternary ammonium hydroxide, such as $\phi N(CH_3)_3OH$.

Again, diazonium chloride and nitrate have a neutral reaction; they are not hydrolysed in aqueous solution, while they are ionized to the same high degree as potassium chloride or nitrate, not only in aqueous but also in alcoholic solution[1]; and the cation has almost the same velocity as that of an alkali metal or ammonium.[2] The carbonates, like those of the alkalies, are soluble in water and of a strong alkaline reaction. The double salts[3] resemble those of the alkalies. The platinichlorides, $(ArN_2)_2PtCl_6$, have long been known; and Hantzsch has shown that the diazonium salts give cobaltinitrites and double chlorides with mercuric chloride analogous to those of potassium and ammonium. Further, as will be shown later, the cyanide forms a double salt with silver cyanide, $Ar{\cdot}N_2{\cdot}AgCy_2$, closely resembling in behaviour potassium silver cyanide, $KAgCy_2$.

A direct determination of the affinity constant of phenyl-diazonium hydrate showed that while it is a decidedly weaker base than tetramethyl-ammonium hydrate it is still nearly seventy times as strong as ammonium hydrate.[4] The strength is greatly diminished by the introduction of negative groups like bromine, but on the other hand it is enormously increased by positive groups such as methyl or methoxyl.[5] Thus anisol ($CH_3O{\cdot}C_6H_4$–) and pseudocumene ($(CH_3)_3{\cdot}C_6H_2$–) diazonium hydrates are, like the alkalies, such strong bases that their strength cannot be exactly measured.

Moreover, it has been shown that the only ions into which the hydrate breaks up are $Ar{\cdot}N_2$ and OH; that is to say, that it is a true hydroxide. This excludes the nitrosamine formula, and leaves us only the choice between $Ar{\cdot}N{=}N{\cdot}OH$ and $Ar{\cdot}N\!\lll^{N}_{OH}$; and the highly basic character of the compounds makes it certain that they must contain pentad nitrogen.

A further point of resemblance between the diazonium and the ammonium compounds is found in the perhalides. These are formed by the action of the halogens on the diazonium halides, and have the composition $Ar{\cdot}N_2{\cdot}Hal_3$. They were originally written on the type $\begin{matrix} Ar{\cdot}N & — & N{\cdot}Br \\ | & & | \\ Br & & Br \end{matrix}$. But it has been shown by

[1] Hantzsch, Davidson, *Ber.* **31.** 1612 (1898).
[2] Hantzsch, *Ber.* **28.** 1740 (1895); Hantzsch, Davidson, l. c.
[3] Hantzsch, Danziger, *Ber.* **30.** 2529 (1897).
[4] Hantzsch, Davidson, l. c.
[5] Hantzsch, Engler, *Ber.* **33.** 2147 (1900).

Hantzsch [1] that they are strictly analogous to the alkaline perhalides, such as KI_3. The diazonium perhalides, like those of the alkalies, are coloured, are not very soluble in most solvents, and readily break up again into the simple halide and free halogen. The resemblance is most marked between the diazonium compounds and those of caesium. Taking the three halogens, chlorine, bromine, and iodine, and neglecting structural or stereoisomerism, ten compounds $X{\cdot}Hal_3$ are possible. Of these in the diazonium series nine are known—all but $-Cl_3$, and in the caesium series eight—all but $-Cl_3$ and $-I_2Cl$. The similarity in colour is most striking. In both series you start with a blue-black almost opaque tri-iodide, and the colour gets lighter as the atomic weight of the halogen diminishes, passing through red, orange ($-Br_3$), and yellow, and ending with the pale yellow $-Cl_2Br$. In colour and in stability the corresponding members of the two series are almost identical. A further argument for their being diazonium compounds and not tri-haloid hydrazines is that on the latter hypothesis they should give structural isomers according to the order in which the halogens are introduced :—

$$\begin{array}{rcl} \mathrm{Ar{\cdot}N{=}N{\cdot}Cl} & & \mathrm{Ar{\cdot}N(Cl){-}N(I){\cdot}Br} \\ + \quad \mathrm{Br{\cdot}I} & = & \end{array} ,$$

and

$$\begin{array}{rcl} \mathrm{Ar{\cdot}N{=}N{\cdot}Br} & & \mathrm{Ar{\cdot}N(Br){-}N(I){\cdot}Cl} \\ + \quad \mathrm{Cl{\cdot}I} & = & \end{array} ;$$

but no such isomers have ever been obtained.

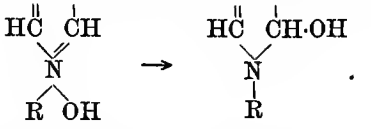
It is clear then that a solution of a diazonium salt closely resembles that of an alkali or compound ammonium salt ; and that just as the latter contains potassium ions or $X{\cdot}\dot{N}{\equiv}H_3$ ions, so the former must contain diazonium ions, $Ar{\cdot}\dot{N}{\equiv}N$. But it does not necessarily follow from this that the undissociated part consists wholly of the compound $Ar{\cdot}N\langle\!\langle^{N}_{X}$ (where X is hydroxyl or the acid radical). An aqueous solution of ammonia contains the ions NH_4 and OH ; but we know that the undissociated NH_4OH breaks up in the solution, to the extent of about two-thirds, into ammonia and water, so that we have an equilibrium :—

$$NH'_4 + OH' \rightleftharpoons NH_4OH \rightleftharpoons NH_3 + H_2O.$$

Now in the case of the undissociated diazonium hydroxide we cannot have this precise change with loss of water, but there is every probability of a change of another kind. It has been shown that all quaternary ammonium hydroxides in which the nitrogen is either doubly linked to carbon, or forms part of a ring, are liable to a peculiar transformation in the presence of a base, the hydroxyl migrating from the nitrogen to another part of the molecule, forming a substance which is no longer a base. In other words they are pseudo-bases. Of the first kind we have already had an example in the triphenyl-methane dyes, where the highly ionized salt, $X_2{\cdot}C{=}C_6H_4{=}NH_2{\cdot}Cl$, on treatment with alkali first gives the corresponding hydroxide $X_2{\cdot}C{=}C_6H_4{=}NH_2{\cdot}OH$, which then changes spontaneously into the undissociated carbinol $X_2C(OH){\cdot}C_6H_4{\cdot}NH_2$. That is, the nitrogen becomes triad through the migration of the hydroxyl to another atom,

[1] *Ber.* **28.** 2754 (1895).

and a non-basic substance is formed. Another such case is that of the pyridonium salts, where the base changes over into the non-basic oxy-pyridine:—



Now diazonium hydroxide is a substance peculiarly adapted for this kind of ionization-isomerism. The basic nitrogen is triply linked to another nitrogen atom, and it is quite probable that in the presence of a base the hydroxyl (of the undissociated portion) may, at any rate partially, migrate to this:—

$$Ar{\cdot}N\lessdot^{N}_{OH} \rightarrow Ar{\cdot}N{=}N{\cdot}OH,$$

the body changing, to use Hantzsch's nomenclature, from a diazonium to a diazo-hydrate. This change is not hypothetical. It is absolutely required to explain the extraordinary behaviour of diazobenzene hydrate. It has been shown that the strongest argument for the diazonium structure of the dissociated part of the molecule is its powerfully basic character. A diazo-hydroxide would be a weak base, like hydroxylamine. But though it is so strong a base, yet it is capable of forming a salt with potash, the normal diazotate. If the solution of the base is treated with a solution of potash, there is a considerable evolution of heat, and measurements of conductivity show that with a not very large excess of potash it is completely converted into such a salt. That is to say, this body, which behaves as a base in some derivatives as strong as potash, is also capable of acting as a rather weak acid. Now we do know of some very weak bases which are able to act also as weak acids, X·OH giving either cations X or anions X·O′; these are the so-called amphoteric electrolytes, such as the hydroxides of aluminium, zinc, lead, and tin. But these bodies differ from the diazo-compounds in being only weak bases and excessively weak acids, their alkaline salts being often so unstable that they cannot be obtained in the solid form. A compound, $Ar{\cdot}N\lessdot^{N}_{OK}$, would not be analogous to such compounds as these, but rather to an alkaline oxide (anhydride) like K_2O. It could only exist in the absence of water, whereas the diazotates are distinct salts, derived from a weak but not excessively weak acid, $Ar{\cdot}N_2OH$. This unique behaviour of diazobenzene hydrate must be due to isomerism. The substance which reacts as a strong base must have a different structure from that which reacts as a weak acid; and if so, it is clear that the base must be the diazonium compound $Ar{\cdot}N\lessdot^{N}_{OH}$, analogous to ammonium hydrate, and the weak acid the diazo-body Ar·N=N·OH, corresponding to hydroxylamine. This hypothesis will also account for the unusual behaviour of sodium normal diazotate. This body, as the salt of a weak acid, is hydrolysed in water to an extent which can be determined by conductivity measurements. But the hydrolysis increases with the dilution enormously faster than in any other known case. It is hard to see how this can be explained except by supposing that the equilibrium is destroyed by the weak acid first liberated going over into the ions of the strong diazonium base.

So far, then, we may conclude that the mineral acid salts of diazobenzene have the diazonium structure, but that on addition of a base the hydrate which is first formed changes over to give the alkaline salts of the weakly acidic diazohydrate Ar·N=N·OH, which are the normal diazotates.

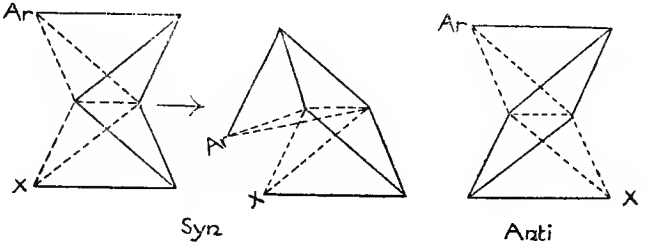
But, as Hantzsch pointed out in his original paper, a substance of this latter structure should exist in two stereoisomeric forms, $\begin{matrix}\text{Ar·N}\\ \|\\ \text{KO·N}\end{matrix}$ and $\begin{matrix}\text{Ar·N}\\ \|\\ \text{N·OK}\end{matrix}$. Now in this case of the alkaline diazotates we have two series of compounds—the normal and the iso—for which two types of formulae must be found. We have seen that the normal salts cannot be true diazonium compounds, because so strong a base could not form salts with another strong base. This is even more obviously true of the iso-diazotates, since the acid from which they are derived must be stronger than that which gives the normal compounds, as they are less hydrolysed. There are therefore three formulae possible for the normal and iso-diazotates :—

$\begin{matrix}\text{Ar·N}\\ \|\\ \text{KO·N}\end{matrix}$	$\begin{matrix}\text{Ar·N}\\ \|\\ \text{N·OK}\end{matrix}$	Ar·NK·N:O.
Syn-diazo.	Anti-diazo.	Nitrosamine.

The third of these formulae is on various grounds very improbable. The isomerism of the alkaline salts is repeated in other classes of derivatives, such as the cyanides and sulphonates ; and any explanation must apply to these as well. But it is evident that the cyanides and sulphonates cannot be given a structure analogous to that of the nitrosamines. Moreover, as will be shown later, the nitrosamines can actually be prepared, and they have quite different properties. Further, a more detailed examination of the chemistry of the diazo-compounds proper—as opposed, that is, to the diazonium derivatives—shows that their isomerism resembles that of stereo- rather than structural isomers. The normal and iso-diazotates (the alkaline salts) are colourless salts, which both form in aqueous solution the isomeric ions $Ar·N_2O'$, but are also to some extent hydrolysed, the normal more than the iso. Their reactions are practically all similar in kind, but the iso react much less readily in most cases. Both classes are easily reduced to hydrazines, and are converted by benzoyl chloride into nitrosoanilides, Ar·N(CO·ϕ)·NO. Both give on oxidation the salts of a nitramic acid, as diazobenzenic acid, $Ar·N_2O·OM$. The same resemblances are shown by the isomeric cyanides and sulphonates. This indicates that the same differences condition the isomerism in all three cases (of the diazotates, cyanides, and sulphonates) ; and the fact that these are differences rather in degree than in kind points to stereoisomerism. A further consideration shows that they can easily be explained on stereo-chemical grounds.

If we draw the structure of the syn- and anti-diazo-compounds on the basis of the usual tetrahedral models, we get figures corresponding to those for fumaric and maleic acids. But there is a remarkable difference between the two cases. In the latter case the two doubly linked carbon atoms are in both modifications more or less symmetrically related to the rest of the molecule. But in the diazo-compounds this is not so. In the syn-compound the two nitrogen atoms must lie wholly on one side and the other two groups on the other. Moreover, if we

suppose, as is generally done, that the three valencies of the doubly linked trivalent nitrogen act from one point of a tetrahedron towards the other three, it is clear from the model that the position of least strain for the syn-compound is that in which the two nitrogen atoms are inclined towards one another, and the two groups attached to them are brought close together; and that even here there will be considerable strain in Baeyer's sense; while in the anti-compound no such strain will exist:—



There is thus an essential difference between the two classes of isomers in the diazo-compounds which does not occur either in the case of fumaric and maleic isomerism or in that of the oximes: namely, that the syn-compounds are necessarily in a state of much greater strain than the anti-. They will therefore be the less stable class, since the strain will endeavour to relieve itself. This it can do in two ways: either by changing into the more stable anti-isomer, or by splitting off the nitrogen entirely:—

$$Ar{\cdot}N_2{\cdot}X \;=\; Ar{\cdot}X + N_2.$$

We should further expect to find that the syn-form was only capable of existence when the second group X attached to it was a small one; as otherwise the two nitrogen atoms would not be able to turn over towards one another sufficiently. And this agrees with experience: the only comparatively stable syn-compounds are the diazotates and the cyanides (X = OM or CN). The syn-sulphonates ($X = SO_3M$) are much less stable, while compounds like the syn-diazoamino bodies (X = NH·Ar) appear scarcely to exist at all.

There are several methods for determining whether a given diazo-compound belongs to the syn- or the anti-series. If both isomers are known, we can say that the syn-, as it has the largest energy content, must be the most reactive of the two. It will be the more explosive, and will be the more readily reduced to hydrazines and oxidized to nitramines and so forth. All these properties are those of the normal as opposed to the iso-diazotates; so that it is clear that the normal are the syn- and the iso the anti-isomers. It is also found that the syn- are the more soluble and have the lower melting-points.

A reaction which is much used for distinguishing between the two classes is that of coupling, i.e. of combining with amines or phenols to give azo-dyes. This always occurs more easily with the syn-compound. Indeed, it was at first supposed that the anti-compounds did not couple at all, but Hantzsch has shown that they always do so, though often very slowly. In other cases, however, they couple quite rapidly, so that this test is not absolutely trustworthy except

where both isomers are known; but then it is invariably found that the syn-compound couples with the greatest rapidity.

Again, the typical diazo decomposition into Ar·X and nitrogen is, as has been pointed out, peculiar to the syn-series; and accordingly we find that it is only the normal diazotates which break up easily in this way; the anti- or iso-compounds decompose much more slowly, and require a higher temperature, which probably converts them first into the syn-isomers.

It is evident, then, that the alkaline diazotates are all true diazo-compounds, and that the so-called normal series, which are the first product of the action of alkali on a diazonium salt, are the syn-compounds, while the iso-diazotates, into which these can be converted, belong to the anti-series.

There remains to consider the constitution of the normal and iso-diazo-hydrates, which are got by the action of acid on the corresponding diazotates. We have already seen that the diazonium hydrate, which may be obtained in solution by treating a solution of a diazonium salt with silver oxide, is a strong base. But we should expect that we might be able to get two isomers of this, the syn-diazo-hydrate and the anti-diazo-hydrate, by the action of acid on the two diazotates. It was formerly supposed that this was the case; but Hantzsch has shown that the true syn-diazo-hydrates cannot be isolated at all, partly because of the ease with which they break up into phenol and nitrogen, and partly because they change with great readiness into their isomers, the diazonium hydrates and the anti-diazo-hydrates. We may, however, infer from the hydrolysis of the syn-diazotates in solution that they are weak acids. The anti-diazo-hydrates are obtained by precipitating the solution of an anti-diazotate with the calculated quantity of acetic acid at a low temperature. They are colourless crystalline compounds, which are very unstable, and are converted even by dissolving in water into the nitrosamines:—

$$\mathrm{Ar{\cdot}N(N{\cdot}OH)} \rightarrow \mathrm{Ar{\cdot}N(H){-}N{=}O}.$$

It is, however, possible, by taking proper precautions, to isolate and examine these anti-diazo-hydrates. They behave as true acids. They react as hydroxyl compounds with phosphorus pentachloride, with acid chlorides, and with phenyl isocyanate; and they give the ammonia reaction. They also couple fairly rapidly with phenols.

If an anti-diazotate is treated with acid without special precautions, or if an anti-diazo-hydrate is allowed to stand, the nitrosamine is produced. Owing to this fact, the diazotate behaves at the ordinary temperature as the salt of a pseudo-acid. Its solution, when treated with an equivalent of hydrochloric acid, has the conductivity of the potassium chloride which it contains. The nitrosamines are yellow crystalline compounds, rather sparingly soluble in water, and easily in organic solvents. As pseudo-acids they have a neutral reaction, but neutralize an alkali; and they do not give the ammonia reaction. They do not react with phosphorus pentachloride in the cold, and hence do not contain a hydroxyl group. They couple very slowly with phenols. Mineral acids in the presence of water convert them into diazonium salts, but dry hydrochloric acid combines

with them in ethereal solution without isomeric change to give the nitrosamine salt Ar·NH·NO·HCl.

It is thus evident that the mineral acid salts of the diazo-compounds have the diazonium structure, and when treated with an equivalent of alkali yield a solution of the diazonium hydrate, which contains the ions $\text{Ar·}\dot{\text{N}}{\equiv}\text{N}$ and OH′, while the undissociated part consists partly of the true diazonium hydrate $\text{Ar·N}\langle^{\equiv\text{N}}_{\text{OH}}$ and partly of the feebly acidic syn-diazo-hydrate $\begin{matrix}\text{Ar·N}\\ \|\\ \text{HO·N}\end{matrix}$. This explains why the same normal diazo-hydrate solution is completely converted by a mineral acid into a diazonium salt, and by excess of alkali into a normal (syn-) diazotate. If the solution is heated with excess of alkali, the syn-diazotate is converted into the anti-(iso)-diazotate :—

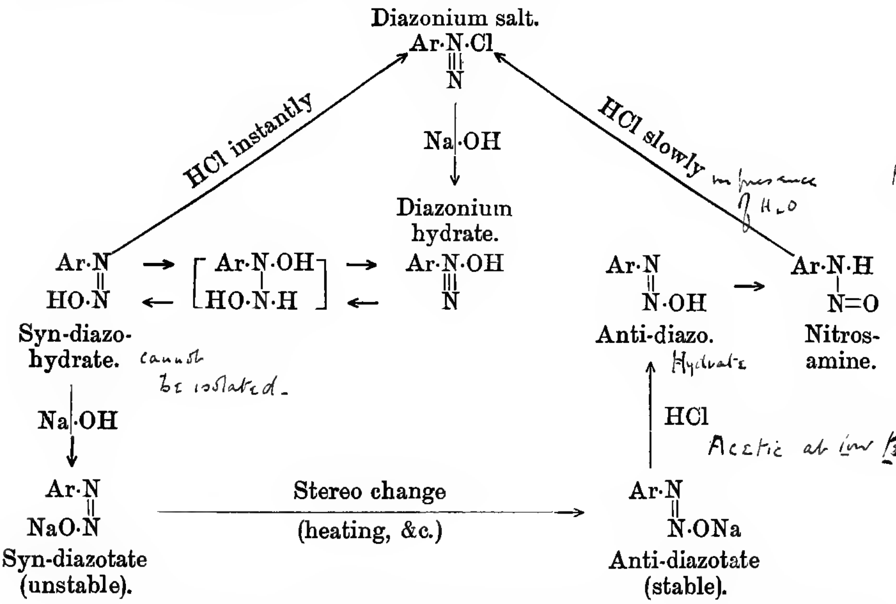
$$\begin{matrix}\text{Ar·N}\\ \|\\ \text{KO·N}\end{matrix} \rightarrow \begin{matrix}\text{Ar·N}\\ \|\\ \text{N·OK}\end{matrix},$$

and when this is treated with an equivalent of acid it gives the very unstable anti-diazo-hydrate, which rapidly goes over into the non-acidic-nitrosamine :—

$$\begin{matrix}\text{Ar·N}\\ \|\\ \text{N·OH}\end{matrix} \rightarrow \text{Ar·NH·NO}.$$

It is to be noticed that whereas the syn-diazo-hydrate is converted by a mineral acid into the diazonium salt too quickly for the progress of the reaction to be observed, the iso-diazo-hydrate only changes slowly, as may be seen by measuring the conductivity.

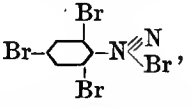
Hantzsch has expressed these rather complicated relationships in the form of a diagram, which renders them somewhat clearer :—



These are the main outlines of Hantzsch's theory of the diazo-compounds.

There are a large number of smaller points, some of which deserve further consideration.

In the first place, there is the question of the structure of the solid salts of the mineral acids. What has hitherto been discussed is their structure in solution. Now they differ very greatly both in colour and in stability, and these two properties always go together, the darkest salts being the most readily exploded. Thus, to take a striking example, 2,4,6-tribrom-phenyl-diazonium bromide,



is deep orange-red and excessively explosive, while the corresponding nitrate is colourless and can scarcely be made to explode at all. If we tabulate the compounds in the following way:—

	Chloride	Bromide	Thiocyanate	Iodide
Trimethyl-benzene diazonium				
Methoxy- ,, ,,				
Benzene ,,				
Monobromo- ,, ,,				
Dibromo- ,, ,,				
Tribromo- ,, ,,				

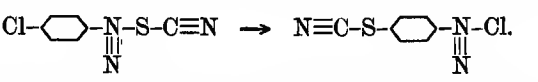
we find that travelling in the direction of the arrows, either downwards or from left to right, we always get an increase of colour and of explosiveness.[1] The less basic the diazonium compound is, the less explosive and coloured its salts are; and as the atomic weight of the halogen increases, these qualities increase also. This indicates a possible difference of constitution, and Hantzsch ingeniously suggests that the solid is a solid solution of the diazonium salt and the syn-diazo-compound. We know that the diazonium salt changes very easily into the diazo; we know that in the case of the cyanides the diazonium is less reactive and is colourless, while the syn-diazo is more reactive and coloured; and we know that the more basic the group is the stronger is the tendency under all conditions to form the diazonium compound. Further, it is obvious that a diazo-halide, having the halogen attached to trivalent nitrogen, would share the explosiveness of the nitrogen halides. It is remarkable that the equilibrium between the two forms in the solid solution seems to be displaced in the diazonium direction by a lowering of temperature. Many of the halides are almost colourless at $-60°$, and their colour deepens continuously as the temperature rises.[2]

This conception of a solid tautomeric substance existing as a solid solution of the two forms has subsequently been extended by Hantzsch to other cases, and in particular to the nitrophenols (p. 174); and he has accumulated a considerable amount of evidence in its favour.

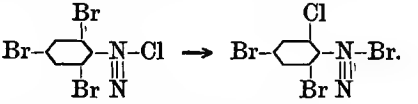
The diazonium salts have a remarkable power of exchanging the acid radical for a substituent in the ortho or para position on the nucleus. This was first

[1] Hantzsch, *Ber.* **33.** 2179 (1900). [2] Hantzsch, Euler, *Ber.* **34.** 4166 (1901).

discovered by Hantzsch and Hirsch[1] in the case of the thiocyanate of *p*-chlorodiazobenzene: in alcoholic solution the chlorine and the thiocyanogen groups change places:—



The chlorides[2] behave in the same way, though less readily, the change only occurring when there are at least two halogen atoms in the ortho or para position: halogens in the meta position have no effect. The velocity of this change has been measured by Hantzsch and Smythe,[3] by removing portions of the solution and precipitating with silver nitrate: the proportion of bromide and chloride in the precipitate was determined by converting a weighed quantity into the chloride in a stream of chlorine. They find that the reaction is roughly of the first order, the constant falling off slightly with dilution. It is slowest in water, more rapid in methyl alcohol, still more so in acetic acid, and quickest in ethyl alcohol, being thus greater the less the dissociating power of the medium. From these facts Hantzsch infers that it is not the ions which change, but the undissociated salt:—



We may assume that, as in practically all cases of the tautomeric change of an ionizable substance, the amount of change is proportional to the concentration of the undissociated part, or to the product of the concentrations of the two ions, which both come to the same thing.[4] The mono-halogen derivatives, whether ortho or para, will not react at all; the di- do so much less easily than the tri-. The chlorine changes places with an ortho-bromine atom more easily than with a para. It is remarkable that the presence of a methyl group on the nucleus in any position, even meta, delays the reaction. The temperature coefficient of the velocity, as in other cases of tautomeric change, is unusually high, being about five for ten degrees.

Cyanogen compounds

Perhaps the most striking confirmation of Hantzsch's views on the diazo-compounds is to be found in their application to the cyanides, which he has investigated in great detail. These cyanides exist in three distinct series. If a diazonium chloride, particularly one with negative substituents in the ring, such as the dibromo-compound, is dissolved in water and an equivalent of potassium cyanide added, a precipitate is obtained of what is known as a normal cyanide. The normal cyanides are more stable than the diazonium salts, but they decompose easily, form the aryl nitriles with copper powder, couple with β-naphthol to azo-dyes, &c. On standing in the solid state, or in alcoholic solution, or on heating in alcoholic solution (according to the precise compound employed), they change over into the isomeric iso-diazo-cyanides—much more stable bodies, which do not give nitriles or azo-dyes, or only do so with difficulty.

These two classes resemble one another in many ways. Besides the easy conversion of one into the other, their reactions are in many respects identical,

[1] *Ber.* **29.** 947 (1896); **31.** 1253 (1898).
[2] Hantzsch, *Ber.* **30.** 2334 (1897).
[3] *Ber.* **33.** 505 (1900).
[4] See p. 184.

and so are their molecular solution volumes, as determined by Traube's method. They always behave as cyanogen and never as isocyanogen derivatives. But their behaviour is totally at variance with what we should expect from a diazonium compound. Such a body, $Ar{\cdot}N\langle^{N}_{CN}$, like $Ar{\cdot}N\langle^{N}_{Cl}$, should closely resemble the cyanides of potassium and tetramethyl-ammonium. But these last are highly ionized and hydrolysed salts, colourless, easily soluble in water, sparingly in organic solvents, and decomposed with evolution of prussic acid by acetic and even by carbonic acid. The diazo-cyanides, both normal and iso, are quite different. They are coloured, volatile in steam, scarcely soluble in water but easily in organic solvents, not directly decomposed (i.e. with evolution of prussic acid) except by the strongest acids. They are not ionized at all, and in fact are not in any respect to be compared to salts. On the contrary their behaviour is rather that of organic cyanides (nitriles), as is shown in their saponification to amides and acids; and of azo-compounds, as in their colour and volatility in steam. Considering the close resemblance between the diazonium salts and those of the quaternary ammoniums and the alkalies, we cannot doubt that normal and iso-diazo-cyanides are not diazonium compounds at all, but are diazo-compounds, with the formula $Ar{\cdot}N{=}N{\cdot}CN$; and as the differences between the two series correspond closely to those between the normal and iso-diazotates (stability, reactivity, coupling power), we must conclude that the normal low melting unstable reactive compounds are the syn-, and the iso-, which are comparatively stable and inactive, are the anti-isomers:—

$Ar{\cdot}N$ normal, $Ar{\cdot}N$ iso,
$\|$ $\|$
$NC{\cdot}N$ syn-diazo. $N{\cdot}CN$ anti-diazo.

A particularly strong proof of the formulae is the fact that it is only the normal which lose nitrogen to form the nitrile:—

$$\begin{matrix} Ar{\cdot}N \\ \| \\ NC{\cdot}N \end{matrix} \rightarrow \begin{matrix} Ar \\ | \\ NC \end{matrix} + \begin{matrix} N \\ \| \\ N \end{matrix}.$$

Besides these two series of syn- and anti-diazo-cyanides there exists a third, which is of a totally different character. The diazo-cyanides of anisol and pseudocumene (i.e. of the most basic compounds), when solid or when dissolved in indifferent organic solvents or in alcohol, behave entirely as syn-diazo-cyanides. They are coloured, they are not dissociated in alcoholic solution, and they are not salts. But when they are dissolved in water they give a colourless solution which is an excellent conductor—is highly ionized—and is decomposed by acetic or carbonic acid. (It is to be noticed that this is a curious inversion of the usual order, where the ionized tautomer is coloured, and the non-ionized colourless.) The conductivity of these bodies is of the same order as that of potassium cyanide, which they resemble in every respect. These are clearly the true diazonium cyanides, $Ar{\cdot}N\langle^{N}_{CN}$. The investigation of the ultra-violet absorption of these bodies confirms this conclusion, the spectra of the syn- and anti-diazo-cyanides being almost identical, while those of the diazonium compounds are quite different.[1]

[1] Dobbie, Tinkler, *J. C. S.* **1905.** 273.

With other diazo-compounds which give a less positive diazonium group, the tendency to form a diazonium cyanide is less. Ordinary diazobenzene cyanide in aqueous solution gives an equilibrium between the undissociated syn-diazo and the dissociated diazonium; whereas compounds containing negative substituents, such as the di- and tri-bromo-bodies, are present in aqueous solution almost if not quite entirely as syn-diazo-cyanides. In fact we can compare a whole series of diazo-compounds, starting with the anisol and pseudocumene derivatives, and passing through diazobenzene itself to the mono-, di-, and tri-bromo-bodies: and as we go down the series we find that the basicity of the diazonium hydrate diminishes, and with it the dissociation of the cyanide in aqueous solution, and also its solubility in and decomposition by acids. The same influences which cause the normal diazo-hydrate—the syn-diazo-hydrate—to change into the dissociated diazonium hydrate also cause the syn-diazo-cyanide to change into the dissociated diazonium cyanide.

The diazonium cyanides are very difficult to isolate. Like potassium cyanide they are largely hydrolysed in solution, i. e. the solution contains a considerable amount of hydroxyl ions; and like diazonium hydrate, only to a still greater extent, they are isomerized by hydroxyl ions to form syn-diazo-cyanides. Moreover, these latter are much less soluble in water, and so crystallize out first.

They can, however, be obtained as double cyanides with silver cyanide, $Ar{\cdot}N\!\lll\!\begin{matrix}N\\CN\end{matrix}$, AgCN. These are colourless soluble neutral salts, decomposed by acetic acid to form nitrogen, hydrocyanic acid, and a phenol, with precipitation of silver cyanide: in other words, strictly analogous to potassium silver cyanide, $KAgCy_2$.

By treating pure anisol-diazonium hydrate at 0° with excess of a very concentrated prussic acid solution, and evaporating the solution in vacuo over phosphorus pentoxide at 0°, Hantzsch succeeded in obtaining crystals of the composition $Ar{\cdot}N_2{\cdot}CN$, HCN, H_2O, which appear to be the solid diazonium cyanide. It forms a highly dissociated solution in water, with a conductivity nearly as high as that of potassium cyanide, which has all the reactions of a diazonium cyanide solution, and which, when treated with a little alkali, gives a yellow precipitate of the syn-diazo-cyanide.

Theory of the typical diazo-reactions

It remains to consider what explanation this theory has to offer of the mechanism of those reactions in which the diazo complex is eliminated and replaced by a different group. There is an obvious peculiarity about them, in that they scarcely ever occur directly, according to the equation:—

$$Ar{\cdot}N_2{\cdot}X = Ar{\cdot}X + N_2,$$

but almost always require the presence of another substance (water, copper powder, &c.), and hence proceed thus:—

$$Ar{\cdot}N_2{\cdot}X + H{\cdot}R = Ar{\cdot}R + H{\cdot}X + N_2.$$

Now it is found by experiment that the only bodies which decompose directly are the syn-diazo-compounds, and that the diazonium compounds always do so indirectly, in accordance with the second equation. This is illustrated by the

case of the sulphonates and the cyanides, and also, as we have seen, of the halides, where the most easily decomposed are the most deeply coloured, i. e. are those which contain the largest proportion of the syn-diazo-compound.

The indirect decomposition of the diazonium compounds is shown in the ordinary diazo-reactions, such as the formation of phenols with water, and of phenol ethers with alcohol. The first of these reactions, the formation of phenol and nitrogen in aqueous solution, has been the subject of several investigations.[1] The method used in all cases was to determine the amount of change by measuring the volume of nitrogen given off. It was found that the reaction was monomolecular, that is, the amount of change was proportional to the quantity of diazonium salt present. It was the same for the chloride, bromide, sulphate, nitrate, and oxalate: it was unaffected by excess of mineral acid, unless this was very large. Substituents on the nucleus, especially in the ortho position, whether positive or negative, diminish the velocity. The case of the iodide is peculiar. Its decomposition is much more rapid, is greatly increased by the presence of light (as indeed are all diazo-reactions),[2] and owing to the occurrence of side reactions no definite constants can be obtained. In the case of the chloride, Hantzsch and Thompson[3] have shown that the decomposition is slower if the salt is dissolved immediately after its preparation, than if it is kept for some time in a desiccator, although no visible change and no loss of weight take place. This must be due to the disappearance of some negative catalyst, whose nature is, however, unknown.

As regards the mechanism of the reaction, the simplest hypothesis is that it is due to hydrolysis:—

$$\mathrm{Ar{\cdot}N{\cdot}Cl \;(\equiv N) \xrightarrow{H_2O} Ar{\cdot}N{\cdot}OH \;(\equiv N) \rightarrow Ar{\cdot}OH + N \equiv N .}$$

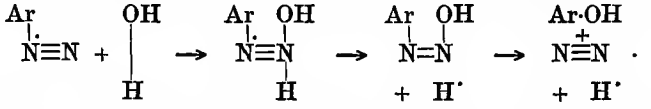
But if this were so, the velocity would be greater the weaker the diazonium, whereas it is independent of this. Further, the hydrochloric acid liberated in the reaction would diminish the hydrolysis, and therefore the velocity, and the monomolecular constant would not be maintained; moreover, the addition of excess of acid at the beginning of the reaction would greatly diminish the velocity, which it does not. Hence the reaction cannot be due to hydrolysis, since its rate depends on the concentration not of the hydrolysed but of the dissociated part of the compound, i.e. of the diazonium ion. But it is quite possible that some addition reaction takes place, for example, with the water, whose concentration remains constant during the reaction. And the fact that in all these reactions the presence of another substance is required points clearly to the occurrence of some such addition reaction. It is easy to see how this would happen. We may suppose that water is first added to the diazonium molecule, and then hydrochloric acid split off:—

$$\mathrm{Ar{\cdot}N{=}N{\cdot}Cl + H{\cdot}OH \rightarrow Ar{\cdot}N{=}N{\cdot}Cl{\cdot}H \rightarrow Ar{\cdot}N{=}N{\cdot}Cl{\cdot}H \rightarrow Ar{\cdot}OH + N{\equiv}N{\cdot}Cl{\cdot}H .}$$

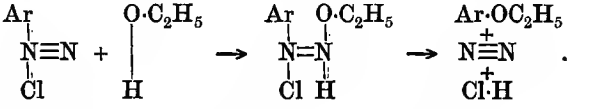
why not this HCl diminish velocity also?

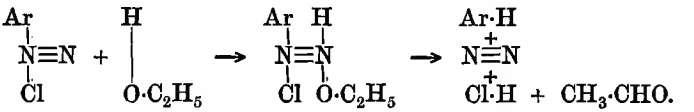
[1] Hantzsch, Oswald, *Ber.* **33.** 2528 (1900); Euler, *Ann.* **325.** 295 (1902); Cain, *J. C. S.* **1902.** 1412; **1903.** 470; Schwalbe, *Ber.* **38.** 2196, 3071 (1905); Cain, ib. 2511; Hantzsch, Thompson, *Ber.* **41.** 3519 (1908). [2] Orton, Coates, *J. C. S.* **1907.** 35. [3] l. c.

Addition-compounds such as are here assumed have been found to exist in some cases; and we know that the syn-diazo-compound which would be formed breaks up in this way into nitrogen and phenol. Since it is found that the velocity is in most cases independent of the acid radical present (provided that it is the radical of a strong acid), it is more correct to formulate the reaction as being due to the diazonium ion, so that the anion does not appear in it at all:—



A peculiarly complicated case is presented by the reaction with alcohol, because this may go, as we have seen, in two directions, giving either the hydrocarbon or the phenol ether. Both these results are easily explained on Hantzsch's theory. It has been shown that the normal course of the reaction is to give the phenol ether: this is the main product with monovalent alcohols, and the only product with the polyvalent, such as glycerine. The formation of hydrocarbons is only the main reaction when there are negative substituents present on the nucleus. But if these are numerous, as in the tri-bromo-compound, the phenol ether is not formed at all, even with dilute alcohol. Now it is clear that on the addition hypothesis the alcohol can attach itself in two ways, and one of these will lead to the formation of a phenol ether, the other to that of a hydrocarbon:—

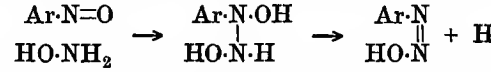
I. 

II. 

Which of these two reactions will occur will depend on the relative attraction of the groups for one another, the positive hydrogen going on the side of the negative chlorine, except when it is attracted away by a strongly negative aryl radical.

By means of similar additive compounds it is possible to explain the other diazo-reactions, such as those of Sandmeyer and Gattermann.

Another reaction which supports this view is the formation of diazo-compounds by the action of hydroxylamine on a nitroso-derivative. Bamberger[1] stated that this produced the iso- or anti-diazotate; but Hantzsch[2] has been able to show that it is really the syn-diazotate which is formed. This is to be expected if we suppose that an intermediate addition-compound is formed, which then loses a hydrogen and a hydroxyl which are near to one another:—



It is evident from the foregoing that the constitution of the diazo-complex in a compound $Ar{\cdot}N_2{\cdot}X$ is mainly determined by the nature of the radical X.

[1] *Ber.* **28.** 1218 (1895). [2] *Ber.* **38.** 2056 (1905).

But it is also affected by the nature of the aryl radical, or in other words by the substituents on the benzene ring. The main directions in which this latter influence acts have been determined by Hantzsch, by the investigation of a large series of compounds. They are as follows. The more important substituents are on the one hand alkyl groups and methoxyl, which render the nucleus more basic, and on the other halogen atoms, which make it more negative or acidic. As regards the relation between diazonium and syn-diazo bodies, it is found that the more basic the nucleus is, the more the diazonium form is favoured; and the more negative, the more the syn-diazo. Thus the trimethyl-diazonium bromide is almost colourless and hardly explosive; the tribromo-diazonium bromide is very explosive and deeply coloured; hence, the former consists mainly of the diazonium, the latter mainly of the syn-diazo. So, too, the trimethyl-diazonium cyanide in aqueous solution is almost wholly in the form of diazonium cyanide ions, of which the tribromo-derivative scarcely forms any. Again, the trimethyl-diazonium hydrate is nearly as strong as potassium hydrate, while the tribromo-diazonium hydrate is weaker than ammonia; that is, it contains very little dissociated diazonium hydrate.

Between these two extreme limits come the other diazo-compounds, for which the same general rule holds: the fewer alkyls or the more halogen atoms there are on the ring, the less the tendency to produce the diazonium form. It is to be observed that the methoxyl group has the same powerful basic influence as the alkyl; a conclusion to which Baeyer has also come from a study of the aromatic oxonium salts.

The relations among the true diazo-compounds between the syn- and anti-series are less regularly affected. In the diazotates the change of syn- into anti- is hindered by methyl groups and promoted by halogens; while in the sulphonates and the cyanides exactly the reverse effect is produced, the more positive compounds changing the most rapidly. The presence of nitro-groups increases the velocity of the change in all cases.

The conversion of the anti-diazo-hydrates into the nitrosamines seems to be hastened by the presence of halogen atoms.

The following summary of the more important results of these investigations may be of service.

We find among the diazo-compounds representatives of all the four possible formulae:—

1. $\overset{\text{Ar}\cdot\text{N}\cdot\text{X}}{\overset{\|\|}{\text{N}}}$. Diazonium. (Blomstrand.)

2, 3. $\overset{\text{Ar}\cdot\text{N}}{\underset{\text{X}\cdot\text{N}}{\|}}$: $\overset{\text{Ar}\cdot\text{N}}{\underset{\text{N}\cdot\text{X}}{\|}}$. Syn- and anti-diazo. (Kekulé-Hantzsch.)

4. Ar·NH·N:O. Nitrosamine. (v. Pechmann.)

The normal salts with strong (mineral) acids are in the solid state mainly diazonium, but partly (especially the halides) solid solutions of diazonium and syn-diazo. In solution they give almost entirely the diazonium ions. The normal hydrates, obtained by treating the salt with an equivalent of acid, are

in solution equilibrium mixtures of the ions of the strongly basic diazonium hydrate, undissociated diazonium hydrate, and undissociated syn-diazo-hydrate. The normal diazotates which this solution forms with alkalies are salts of the weakly acidic syn-diazo-compounds; but on heating, or sometimes on standing at the ordinary temperature, they undergo a stereoisomeric change, giving the iso-diazotates, which are anti-diazo-compounds, derived from the less reactive form, which is more acidic than the syn-. If the iso (anti-) diazo-hydrate is set free, it changes with great ease into the nitrosamine.

The ordinary diazo-reactions which result in the elimination of nitrogen are not reactions of the diazonium salts at all, but of the syn-diazo-bodies formed from them through an additive compound with some other substance present.

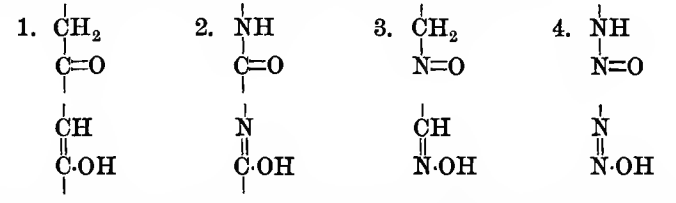
Finally, among the cyanides there are three distinct series, corresponding to all the three possible formulae:—

1. Syn-diazo: generally the most easily formed, especially when there are negative substituents on the ring. They are coloured, insoluble in water, easily soluble in organic solvents, not dissociated, behaving like organic nitriles, and not decomposed except by strong acids. They break up into nitrogen and nitriles directly.

2. Anti-diazo: formed by spontaneous change from 1, which they closely resemble. They are coloured, insoluble in water, soluble in organic solvents, not ionized, not true salts, not decomposed by weak acids. But they are more stable than the syn-, and do not give the nitrile directly.

3. Diazonium: formed from the syn-diazo-compounds with positive substituents on the ring, by dissolving them in water. They are colourless, easily soluble in water, going back in organic solvents into the coloured syn-diazo. They are ionized and hydrolysed in water, are decomposed by weak acids, and are converted into the insoluble syn-diazo-bodies by hydroxyl ions.

With regard to the tautomerism of the anti-diazo-hydrates and the nitrosamines, it is to be noticed that it really belongs to the keto-enolic type, and completes the series of the possible replacements of the carbon in that type by nitrogen. We have the following four groups, all formed on the same plan, and all characterized by the same tendency to tautomerism:—



Of these, the first type provides the classical examples of tautomerism, as in the β-keto-esters and diketones. The second is exemplified in the amides and iso-amides, and in such ring-compounds as isatin. The third type occurs in the nitroparaffins, and in the tautomerism of the secondary or primary nitroso-compounds and the oximes.

CHAPTER XII

AZO-COMPOUNDS, AZOXY-COMPOUNDS, NITRAMINES

The azo-compounds differ from the diazo in having the –N=N– group attached to carbon on both sides. According to this definition the diazo-cyanides are, strictly speaking, azo-compounds, but it is more convenient to treat them as belonging to the diazo-group. The azo-bodies with which we are practically concerned are almost entirely those in which the N_2 group connects two aromatic nuclei. This conditions much greater stability, and excludes the possibility of the complicated isomerism and tautomerism of the diazo-group.

The nomenclature usually adopted for the simpler azo-bodies is to put the word azo between the names of the hydrocarbons from which the two radicals are derived. Thus:—

$CH_3 \cdot C_6H_4 \cdot N=N \cdot \phi$ = Toluene-azo-benzene,
$\phi \cdot N=N \cdot C_6H_4 \cdot N(CH_3)_2$ = Benzene-azo-dimethyl-aniline.

Other systems have been suggested, which are perhaps more convenient in dealing with the more complicated derivatives, and may be used by the specialist who wishes to distinguish the enormous number of azo-dyes. But for ordinary purposes the simpler method will suffice.

The azo-compounds are usually prepared by the moderated reduction of the nitro-compounds in alkaline solution: generally with zinc dust in alcoholic solution in presence of potash, or with sodium amalgam, or more recently by electrolysis. This, of course, yields only the symmetrical bodies. It is worth noticing that the yield is worse the more side chains are present. They may also be obtained by oxidizing the amines in alkaline solution with potassium permanganate or ferricyanide. In this case the yield is better the more side chains there are.

The unsymmetrical compounds are prepared by heating a mixture of an amine and a nitro-derivative with powdered soda to 180–200°, a method devised by Sandmeyer. The first product is the azoxy-compound:—

$$CH_3 \cdot C_6H_4 \cdot NO_2 + H_2N \cdot \phi = CH_3 \cdot C_6H_4 \cdot \underset{\diagdown O \diagup}{N}\!\!-\!\!N \cdot \phi + H_2O.$$

Then one part of the azoxy-body reduces the rest to azo, being itself burnt up in the process.

A formation of theoretical interest is by the action of a nitroso-compound on an amine:—

$$CH_3 \cdot C_6H_4 \cdot NH_2 + O=N \cdot \phi = CH_3 \cdot C_6H_4 \cdot N=N \cdot \phi + H_2O.$$

This corresponds to the formation of a diazo-compound from a nitroso-body and hydroxylamine.

The mixed azo-compounds (containing a fatty as well as an aromatic group)

are got by oxidizing the mixed hydrazo-compounds or symmetrical secondary fatty-aromatic hydrazines with mercuric oxide:—

$$\phi\cdot NH\text{–}NH\cdot CH_3 + O = \phi\cdot N{=}N\cdot CH_3 + H_2O.$$

The aromatic azo-bodies are crystalline substances (some of the mixed derivatives are liquids) of an intense red or orange colour. They distil unchanged at rather high temperatures (azobenzene, for example, at 293°), and they are volatile in steam. They are insoluble in water, alkali, and acid, but dissolve in organic solvents. They are remarkable for their extreme stability; they are not affected by distillation or by boiling with acid or alkali, a striking contrast to the diazo-compounds. As regards their structure, it is obvious that, like the diazo-bodies, they might be either syn- or anti-compounds; from their great stability it is clear that they must be anti-,

$$\begin{matrix} Ar\cdot N \\ \| \\ N\cdot Ar_1 \end{matrix}.$$

No cases of stereoisomerism have yet been observed among them for certain, although there is an instance of isomerism among the aminoazo-compounds, which is very probably to be referred to stereo-causes.

Though they are so stable under ordinary conditions, they are very sensitive to reducing agents, which, if alkaline, convert them into hydrazo-compounds, or, on more energetic reduction, into amines: acid reducing agents generally transform them directly into benzidines. They are even reduced, especially in methyl alcohol solution, by hydrochloric acid, with the formation chiefly of chlorination products of hydrazobenzene and aniline.[1]

Azobenzene, $\phi\cdot N{=}N\cdot\phi$, itself was discovered by Mitscherlich in 1834. It forms fine orange-red crystals, melting at 68° and boiling at 293°. It may be prepared in any of the ways that have been mentioned, and is generally made by reducing azoxybenzene (obtained by the reduction of nitrobenzene in alkaline solution) by distillation with iron filings.

The mixed azo-bodies, in which the N_2 is attached on one side to an aromatic and on the other to a fatty hydrocarbon, are liquids. They resemble the purely fatty azo-bodies, and differ from the purely aromatic, in being able to split off the nitrogen on heating, the two residues combining. This reaction has been made use of by Gomberg for the preparation of tetraphenyl-methane. He made triphenyl-methane-hydrazo-benzene, $\phi_3C\cdot NH\text{–}NH\cdot\phi$, oxidized this to the corresponding azo-body $\phi_3C\cdot N{=}N\cdot\phi$, and by heating a mixture of this with sand obtained, though only in very small quantity, the previously unknown tetraphenyl-methane ϕ_4C.

Another peculiarity of these mixed azo-compounds is that sulphuric acid converts them into the isomeric hydrazones:—

$$\phi\cdot N{=}N\cdot CH_2\cdot CH_3 \longrightarrow \phi\cdot NH\text{–}N{=}CH\cdot CH_3.$$

This has already been mentioned in connexion with the supposed formation of hydrazones by the action of diazo-compounds on the acidic methylene group.

The simplest azo-compound, azomethane, $CH_3\cdot N{=}N\cdot CH_3$, has been prepared quite recently by Thiele,[2] who obtained it by oxidizing hydrazomethane,

[1] Jacobson, *Ann.* **367.** 304 (1909). [2] *Ber.* **42.** 2575 (1909).

$CH_3{\cdot}NH{\cdot}NH{\cdot}CH_3$ (*s*-dimethyl-hydrazine), with potassium chromate. It is a colourless gas with no alkaline reaction, which condenses to a liquid boiling at + 1·5°. The liquid has only a pale yellow colour, in which respect it resembles another purely fatty azo-compound, azoisobutyric ester,[1] $\begin{matrix}(CH_3)_2C\text{–}N\\ |\\ CO_2Et\end{matrix}=\begin{matrix}N\text{–}C(CH_3)_2\\ |\\ CO_2Et\end{matrix}$. It explodes on heating, but if mixed with excess of carbon dioxide decomposes quietly, mainly into ethane and nitrogen :—

$$CH_3{\cdot}N{=}N{\cdot}CH_3 \;=\; CH_3{\cdot}CH_3 + N_2.$$

The alternative formula, that of a hydrazone, $CH_3{\cdot}NH{\cdot}N{=}CH_2$, is excluded by its distinct though pale colour in the liquid state, by its decomposing to give ethane (which is exactly analogous to the formation of tetramethyl succinic ester from azoisobutyric ester, an undoubted azo-body), and by the fact that it is easily reduced to the hydrazo-compound. On the other hand, it is easily broken up by acids into methyl hydrazine and formaldehyde, so that it can readily assume the hydrazone structure. The same thing has been observed with the mixed azo-body, phenyl-azo-ethane, $\phi{\cdot}N{=}N{\cdot}CH_2{\cdot}CH_3$.[2]

The remarkable instability of azo-triphenyl-methane, $\phi_3C{\cdot}N{=}N{\cdot}C\phi_3$, has already been mentioned (p. 255).

By far the most important azo-derivatives are the aminoazo- and oxy-azo-compounds which are used as dyes. Their formation has already been referred to. Practically any primary aromatic amine can be diazotized, and the body so formed can be coupled with any aromatic amine (primary or otherwise) or phenol; so that the number of azo-dyes which can theoretically be prepared is enormous. Already the components described in patents for azo-dyes are sufficient to yield several millions; and the number which could be obtained from all the known amines and phenols amounts to several hundred millions. In comparison with these figures the 75,000 compounds in Beilstein and the 100,000 in Richter's Lexicon appear insignificant.

As the azo-dyes are perhaps the most important and certainly the most numerous class of organic dyes, a few remarks on the process of dyeing may be useful.

The cloth is dyed by bringing it into a solution of the dye in water: this is the dyeing bath. It is therefore necessary to render the dye soluble in water, if it is not so already. This is frequently done by sulphonation, i.e. by introducing an SO_3H group into the nucleus, since all sulphonic acids are soluble in water; the substitution in most cases has little or no effect on the colour. The dyes are divided into two classes, adjective and substantive dyes. A substantive dye is one which is capable of dyeing the fibre as it is, that is, without any previous treatment; an adjective dye requires the use of a mordant. Many dyes are either substantive or adjective according to the fibre used. A great number are substantive to animal fibre (silk or wool) and adjective to vegetable.

As mordants, tannic acid and compounds of it with preparations of antimony are often used. Acid dyes, such as oxy-azo-compounds, are often fixed by first soaking the cloth in a solution of an easily decomposed aluminium, ferric, or

[1] Thiele, Heuser, *Ann.* **290.** 5. (1896).

[2] E. Fischer, *Ber.* **29.** 793 (1896).

chromic salt (especially the acetate), and then passing it through a feebly basic bath or steaming it, so as to separate the oxide of the metal. The dyeing then consists in the formation of an insoluble compound of the dye with the oxide, known as a lack. The colour with many dyes depends on the base used; such dyes are called polychromatic. Thus alizarin dyes red with aluminium salts, violet with ferric, and brown with chromic.

Sometimes the dye is produced on the fibre itself, either by soaking it in a solution of the leuco-base (e.g. indigo-white, which is probably di-indoxyl) and then oxidizing it by exposure to the air; or, in the case of azo-dyes, by passing it successively through solutions of the two components.

The value of a dye depends, of course, on its beauty, on its dyeing power, and on its fastness—its power to resist washing, soap, and light, and in special cases acids, &c.

A dye is necessarily a coloured substance capable of adhering to the fibre; and it, therefore, must have in the molecule two kinds of groups, one giving it colour, and the other giving it this power of adherence. The first of these groupings is known as a chromophor, such as the azo-group, –N=N–, which of itself gives colour, but does not yield a dye; the second is called an auxochrome, but about this there is a certain amount of confusion. The terminology is originally due to Witt, who supposed that certain groups, which he called the chromophors, were essentially colour-producing, but in some cases required the presence of a second group, not in itself coloured, to call out or at least increase the colour. Groups of this second kind he called auxochromes. Subsequently, as the interest of chemists was diverted from the purely scientific question of the cause of colour to the more practical problem of producing dyes, the word auxochrome changed its meaning, and was applied to those groups which give a coloured compound its power of adhering to the fibre. This confusion was increased by the fact that the two most important auxochrome groups in the dyeing sense are hydroxyl and the amine or substituted amine group; and these are also auxochromes in the original Witt sense, of increasing the colour of a compound without reference to its dyeing power. These two groups are both salt-forming, one being basic and the other acidic; but other salt-forming groups, such as CO_2H and SO_3H, will not act in this way.

Another remarkable point about dyes, and, indeed, about coloured organic compounds in general, is that they can be converted by reduction into colourless bodies, the so-called leuco-compounds, which generally go back readily, often even on exposure to the air, into the original dye. The leuco-derivatives of the azo-dyes are the hydrazo-compounds, which themselves are colourless, but are reconverted by the air into the coloured azo-compounds.

The azo-dyes may be divided into two classes, according to the auxochrome (in the dyeing sense) which they contain:—

1. The aminoazo-compounds, with NH_2.
2. The oxy-azo-compounds, with OH.

The first azo-dye put on the market was chrysoidine (from diazobenzene and meta-phenylene-diamine), which was prepared in January, 1876, by an English firm, by the method discovered, of course, by Griess, but developed by O. N. Witt.

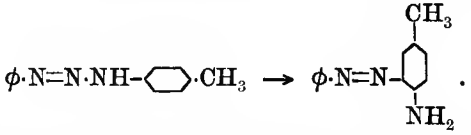
AMINOAZO-COMPOUNDS

In practice the aminoazo-compounds are always prepared by the action of an amine on a diazo-solution. But in many cases this gives first, as an intermediate product, the diazo-amino-body. Direct formation of the aminoazo-compound occurs with a tertiary amine, as it obviously must, and with *m*-diamines in neutral or feebly acid solution. It is also observed with some secondary monamines in presence of mineral acids, while in neutral or acetic acid solution they usually give the diazo-amino. The conversion of the diazo-amino into the aminoazo-body occurs slowly even on standing in alcoholic solution; but it is hastened by the addition of small quantities of the amine salt. If the diazo-amino-compound is treated with an equivalent of the salt of another amine, it is possible to introduce this second amine, e.g.:—

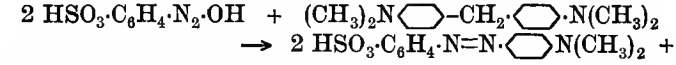
$$CH_3{\cdot}C_6H_4{\cdot}N{=}N{\cdot}NH{\cdot}C_6H_4{\cdot}CH_3 + C_6H_5{\cdot}NH_3Cl = CH_3{\cdot}C_6H_4{\cdot}N{=}N{\cdot}C_6H_4{\cdot}NH_2 + CH_3{\cdot}C_6H_4{\cdot}NH_3Cl.$$

The aminoazo can be prepared directly, under suitable conditions, by acting on excess of the amine with nitrous acid; but this implies the intermediate formation of the diazo and diazo-amino-compounds.

The position taken up by the azo-group on the nucleus of the amine is always para, if this place is open; and it is only in this case that the reaction goes easily. If this place is occupied, the reaction can be brought about, though much less readily, and the azo-group takes up the ortho position:—



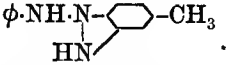
It is remarkable that dialkyl-amines, in which the para position is filled up, usually refuse to give ortho products.[1] Either no reaction takes place, or the para substituent is expelled, and a *p*-aminoazo-compound produced. The most striking case of this is afforded by *p,p*-tetramethyl-diamino-diphenyl-methane, where both the nuclei separate from the methane carbon:—



The structure of the product is determined by energetic reduction, which converts it into a mixture of a monamine and an *o*- or *p*-diamine.

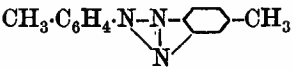
We have thus two classes of aminoazo-compounds, the ortho and the para. They differ so remarkably in behaviour that it has been suggested that they have different constitutions.

The para compounds have the normal behaviour of primary amines, and hence must certainly have the normal aminoazo formula. But the behaviour of the ortho-compounds makes it possible that they contain a closed nitrogen ring, e.g.:—

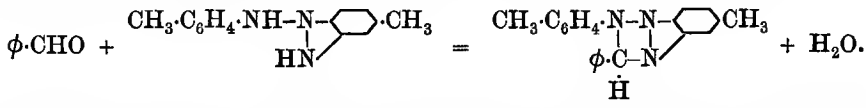


[1] Scharwin, Kaljanov, *Ber.* **41**. 2056 (1908).

For instance, on oxidation they give colourless azimido-compounds such as



Again, whereas the para react with aldehydes like primary amines, giving indifferent compounds which readily decompose again into their components, the ortho give colourless basic substances, stable on heating with acids, which belong to the triazine group:—

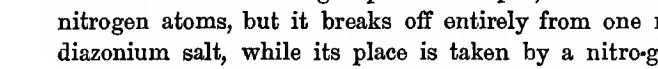


It is to be noticed, however, that these differences are scarcely greater than those between the para and ortho diamines, where no difference of constitution is to be suspected. The peculiarities of the ortho bodies are probably only illustrations of the general tendency of ortho di-substitution-products to form closed rings ('ortho-condensation').

Properties

They are yellow or brown substances, scarcely soluble in water: hence the importance of sulphonation when they are to be used as dyes. They are basic, and easily dissolve in acids to form brilliantly coloured salts, which usually have a different colour from the base; these salts are discussed below. They have the behaviour both of amines and of azo-compounds. As amines they give acyl and alkyl derivatives and salts; and they can be diazotized and used as components for new azo-dyes, producing the dis-azo-compounds. As azo-bodies they can be reduced to hydrazo-compounds and ultimately split up into a monamine and a diamine. If they are boiled for a long time with strong hydrochloric acid the same decomposition occurs, the acid acting like a mixture of free hydrogen and free chlorine (compare the action of hydrochloric acid on quinone chlorimines and tetraphenyl-hydrazine). Thus aminoazo-benzene yields mainly aniline and *p*-phenylene diamine, together with chlorinated hydroquinones such as $C_6HCl_3(OH)_2$.

Another peculiar method of splitting the aminoazo (and also the oxy-azo) compounds into their components is by the action of fuming nitric acid.[1] This is sometimes of use for determining their constitution where the reduction method fails. The azo-group does not split, as it usually does, between the two nitrogen atoms, but it breaks off entirely from one nucleus, appearing as the diazonium salt, while its place is taken by a nitro-group:—



It has been shown by Bamberger[2] that the azoxy-compounds are oxidized to diazo by potassium permanganate, and it is therefore probable that in this case the fuming nitric acid first oxidizes the azo-group to azoxy and then further to the diazo; indeed, simple oxidizing agents such as chromic acid and potassium permanganate will break up azo-compounds in the same way.

[1] O. Schmidt, *Ber.* **38.** 3201, 4022 (1905). [2] *Ber.* **33.** 1957 (1900).

The mineral acid salts of the aminoazo-compounds have recently been investigated by Hantzsch and Hilscher,[1] who have shown that they occur regularly in two series, one yellow and the other violet. An isolated case of this was, indeed, discovered by Thiele some years ago. Which of these two is obtained in any particular case depends both on the aminoazo-compound used and on the acid; nor could any regularities in their influence be discovered. In many cases, however, both the isomeric salts could be isolated, the yellow unstable salt usually crystallizing out first, and the violet stable form later. In the solid state the unstable form does not change over as long as it is kept dry and cold; but on warming, or in presence of traces of free acid, or sometimes even on rubbing, it goes over into the stable form. In solution equilibrium between the two forms is as a rule established at once, the proportions, and hence the colour of the solution, depending on the base and the acid, but very largely on the solvent, indifferent solvents such as chloroform favouring the violet form, and solvents of a higher dielectric constant, like ether and alcohol, the yellow.

As regards the question of structure, that of the orange-yellow series is fairly certain. Their colour is very similar to that of azobenzene itself and the salts of azobenzene-trimethyl-ammonium, $\phi\cdot N{=}N\cdot C_6H_4\cdot N(CH_3)_3X$, which, as it contains no mobile hydrogen atom, must have the true azo-structure, and whose salts are accordingly found to be in all cases orange-yellow. It is therefore certain that these orange-yellow salts of the aminoazo-compounds are also true azo-salts of the type $\phi\cdot N{=}N\cdot C_6H_4\cdot NR_2HX$.

The violet salts are not polymers of the yellow, as was shown by a determination of their molecular weight in solution, which was found to be normal. They are, therefore, true isomers of the yellow form. The hydrazone formula suggested by Auwers,[2] $\overset{\displaystyle H\ \ X}{\overset{\frown}{Ar\cdot NH\cdot N{=}C_6H_4{=}NR}}$, is excluded by the fact that similar salts are given by the dialkyl-aminoazo-bodies. Hantzsch and Hilscher therefore propose the quinoid formula $Ar\cdot NH\cdot N{=}C_6H_4{=}NR_2X$ for the violet modification. While this view is quite probable, it is to be noticed that the relations of these two series of salts are almost precisely the same as those observed in the yellow and red salts of the nitrophenols, the dinitroparaffins, and the α-nitroketones. In these three last-mentioned cases Hantzsch attributes the isomerism with great probability to stereo-chemical causes; and the same explanation will account for the aminoazo-salt if we suppose that the more stable orange-yellow salts belong, like azobenzene, to the anti-series, and the unstable violet salts to the syn-:—

$$\begin{array}{rl} Ar\cdot N & \text{violet,} \\ \| & \\ HXR_2N\cdot C_6H_4\cdot N & \text{unstable} \end{array} \quad : \quad \begin{array}{rl} Ar\cdot N & \\ \| & \\ N\cdot C_6H_4\cdot NR_2HX & \text{orange-yellow, stable.} \end{array}$$

Or perhaps an even closer analogy to these other cases is expressed by a formula such as $Ar{-}NH{-}\underset{\lfloor\!\_\!\_\!\_\!\_\!\_\!\rfloor}{N}{-}C_6H_4{-}NR_2X$, which might also admit of stereoisomerism.

[1] *Ber.* **41.** 1171 (1908); Hantzsch, *Ber.* **42.** 2129 (1909). [2] *Ber.* **33.** 1314 (1900).

OXY-AZO-COMPOUNDS OR AZO-PHENOLS

The symmetrical oxy-azo-compounds may be obtained by the reduction of nitrophenols in alkaline solution; but these are of small practical importance in comparison with the unsymmetrical, which are made by coupling a diazo-solution with a phenol. The reaction takes place practically only in a weakly alkaline solution. In neutral solution it often leads to the formation of nitrogen and a phenol ether; while a great excess of alkali may prevent the reaction altogether, probably from the formation of the isodiazotate. Goldschmidt has shown that the velocity of formation of the dye is proportional to the concentration both of hydrogen and of hydroxyl ions. It is also, of course, affected by the nature both of the phenol and of the diazo-compound. As regards the phenol, it is found that the presence of an azo-group in it hinders the coupling; oxy-azobenzene will couple again to give bis-azo-phenol, $HO{\cdot}C_6H_3(-N{=}N{\cdot}\phi)_2$, but this body is not capable of taking on another azo-group. It is remarkable that the presence of a doubly linked carbon attached to the ring of the phenol has the same effect as an azo-group, so that oxy-cinnamic acids will only couple once and not twice.[1] As regards the influence of the structure of the diazo-body, the reaction velocity is diminished by the introduction of halogens, and increased by that of alkyls; that is, it is greater the more basic the diazo-compounds.

The similarity of the reactions of diazo-compounds with phenols and with amines makes it probable that there may be an intermediate stage in the former case analogous to the diazoamino-bodies in the latter:—

$$\phi{\cdot}N_2{\cdot}OH + HO{\cdot}C_6H_4{\cdot}H \longrightarrow \phi{\cdot}N{=}N{\cdot}O{\cdot}C_6H_4{\cdot}H \longrightarrow HO{\cdot}C_6H_4{\cdot}N{=}N{\cdot}\phi,$$

as was indeed originally suggested by Kekulé. It has been proved by Dimroth[2] that in many cases an intermediate product is formed, to which he attributes a structure of this kind. For instance, *p*-bromophenyl diazonium chloride combines with *p*-nitrophenol to form an unstable substance which soon decomposes with loss of nitrogen, and is at once broken up by acids to give the diazonium salt. If this is heated in the dry state to 80° it goes over into the stable oxy-azo-compound

$$Br{\cdot}C_6H_4{\cdot}N_2{\cdot}O{\cdot}C_6H_4{\cdot}NO_2 \longrightarrow HO{\cdot}C_6H_3(N{=}N{\cdot}C_6H_4{\cdot}Br){\cdot}NO_2.$$

Other similar cases are recorded by Bucherer[3] and by Auwers,[4] who, however, points out, as we have seen already, that the behaviour of these bodies is quite compatible with their being not O-azo-compounds, Ar·N=N·O·Ar, as Dimroth supposes, but merely diazonium salts, $\begin{matrix} Ar{\cdot}N{\cdot}O{\cdot}Ar \\ \| \\ N \end{matrix}$, which would explain why they are formed with peculiar ease from negatively substituted phenols. Whichever view may be right, it is evident that in coupling with phenols the N_2 group first attaches itself to the oxygen, as it does with amines to the nitrogen, and then subsequently passes over to the ring.

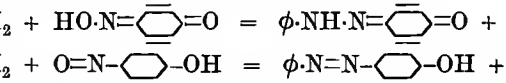
As we have seen, the power of coupling is one of the best tests for dis-

[1] Borsche, Streitberger, *Ber.* **37**. 4116 (1904).
[2] Dimroth, Hartmann, *Ber.* **41**. 4012 (1908).
[3] *Ber.* **42**. 47 (1909).
[4] *Ber.* **41**. 4304 (1908).

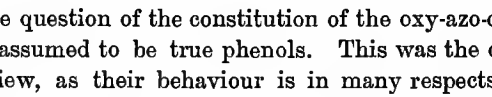
tinguishing between the syn- and anti-diazo-compounds. An anti-compound will couple, but always much more slowly than its syn-isomer.

The following rules govern the position of the azo with respect to the hydroxyl group. If the para position is open it is always taken. If it is occupied and the ortho is open, then that is taken. There are only one or two examples of the ortho position being occupied when the para is open, and a few where one or both of these positions are unoccupied, and where yet no coupling occurs at all. The same applies to the case where a second azo-group is introduced, except that the two will not both take up the ortho position. Coupling in the meta position never occurs at all, and the meta-oxy-azo-compounds can only be got by indirect methods. Para-oxy-benzoic acid couples with diazobenzene to give para-oxy-azobenzene, the carboxyl being eliminated, as also happens in certain benzidine reactions.

There is another method of preparing the oxy-azo-compounds which is of some theoretical interest, and that is by the action of amines on the quinone oximes or nitrosophenols. This can be written in two ways, which illustrate the two possible formulae of the oxy-azo-bodies :—

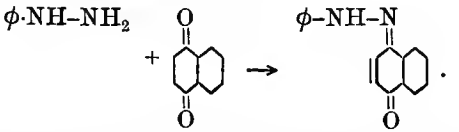


$$\phi\cdot NH_2 + HO\cdot N=\text{C}_6\text{H}_4=O = \phi\cdot NH\cdot N=\text{C}_6\text{H}_4=O + H_2O;$$



$$\phi\cdot NH_2 + O=N-\text{C}_6\text{H}_4-OH = \phi\cdot N=N-\text{C}_6\text{H}_4-OH + H_2O.$$

This raises the question of the constitution of the oxy-azo-compounds, which have so far been assumed to be true phenols. This was the original and is the most probable view, as their behaviour is in many respects that of phenols. The question has, however, been much disputed,[1] and a great deal of work has been devoted to it, especially in recent years, without any very satisfactory results being arrived at. The first doubt as to the correctness of the phenol structure was raised by Liebermann,[2] on the ground of certain differences in behaviour between the ortho and the para series, and by Zincke and Bindewald,[3] who showed that α-naphthoquinone and phenyl-hydrazine gave the same product as that obtained from diazobenzene and α-naphthol: they therefore suggested that the body might really be a hydrazone :—



$$\phi\cdot NH\text{–}NH_2 + \text{C}_{10}\text{H}_6\text{O}_2 \rightarrow \phi\text{–}NH\text{–}N=\text{C}_{10}\text{H}_6=O.$$

Goldschmidt and his pupils[4] then found that the ortho compounds would not react with phenyl isocyanate, and therefore attributed to them the hydrazone (quinoid) structure. Meldola[5] investigated the products of the reduction of the acyl derivatives, and found that in all cases they behaved as if they were a mixture of the two forms; for example, acetyl-*p*-oxy-azobenzene as if it were partly $\phi\cdot N=N\cdot C_6H_4\cdot O\cdot CO\cdot CH_3$ and partly $\phi\cdot N(CO\cdot CH_3)N=C_6H_4=O$. It has since been shown that the acyl groups in these compounds are unexpectedly

[1] A brief and very clear summary of the question is given by Auwers, *Ann.* **360.** 11 (1908).

[2] *Ber.* **16.** 2858 (1883). [3] *Ber.* **17.** 3032 (1884).

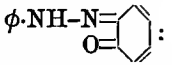
[4] *Ber.* **23.** 487 (1890); **24.** 2300 (1891); **25.** 1324 (1892).

[5] Meldola, Morgan, *J. C. S.* **1889.** 114; Meldola, Hawkins, ib. **1893.** 923; Meldola, Burls, ib. 930; Meldola, Hanes, ib. **1894.** 834.

mobile, and much of the confusion which has arisen is due to the fact that this mobility was not recognized.[1]

Hewitt[2] then investigated the action of substituting agents, especially bromine and nitric acid, on the oxy-azo-compounds, and proved that the para and the ortho derivatives behaved in the same way, and as if they were true phenols.

Jacobson and Honigsberger[3] attacked the problem by preparing the previously unknown meta-oxy-azobenzene, which might be assumed not to have a quinoid structure, and instituted an elaborate comparison of its properties with those of the other two isomers. The results are as follows. The meta and para compounds dissolve in the equivalent quantity of soda, whereas the ortho will only dissolve in a very large excess. In toluene solution the meta and para take up dry ammonia readily, but the ortho not at all. All three bodies form a salt with hydrochloric acid; but the meta and para salts are stable, whereas the ortho salt loses its hydrochloric acid in the air very readily. Again, the molecular weight of the ortho compound, as determined by the freezing-point method in benzene solution, is normal, and independent of the concentration; whereas that of the meta and para rises rapidly with the concentration. In all these cases the meta and para derivatives behave alike, so that as the meta compound is a true phenol we must conclude that the para is so also. But the peculiar behaviour of the ortho compound led Jacobson and Hönigsberger to the view that it was the quinone-hydrazone



at the same time its alkaline salts, which exactly resemble those of the para body, they assumed to be true phenol salts with the structure ϕ·N=N-  -OM. If this view is correct, it is remarkable that it should be the ortho compound which has the strongest tendency to assume the quinoid form, since among the quinones themselves it is the para which is the most easily produced and the most stable. It is, however, doubtful whether the differences which have been enumerated are sufficient to establish the difference of structure. The peculiarities of the ortho compound, some of which have since appeared to be differences in degree rather than in kind, may be merely due to the influence of the hydroxyl in immediate proximity to the azo-group. There is no doubt that in this position the hydroxyl is much less acidic, and in general (perhaps through stereo-hindrance) much less active. This is shown not only in the insolubility of these compounds in alkali (which, however, is less marked in some cases than it is in that of o-oxy-azobenzene), but also, for example, in the ease of methylation by methyl sulphate, a reaction which goes quantitatively in the para series, but with much less ease in the ortho.[4] In the same way, while the para bodies react with diazomethane to give their methyl ethers, the ortho do not react at all[5]; and this last fact cannot be explained by giving them a quinoid structure, since a hydrazone should react with diazomethane through the NH group.

[1] Cf. McPherson, *Ber.* **28**. 2414 (1895); *Am. Ch. J.* **22**. 364 (1899).

[2] Hewitt, *J. C. S.* **1900**. 99; Hewitt, Aston, ib. 712, 810; Hewitt, Fox, ib. **1901**. 49; Hewitt, Lindfield, ib. 155; Hewitt, Phillips, ib. 160; Hewitt, Auld, ib. **1902**. 1202; Hewitt, Walker, ib. **1906**. 182.

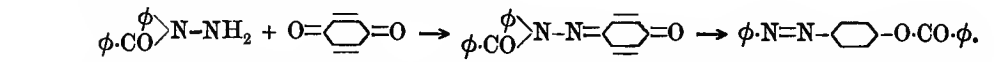
[3] *Ber.* **36**. 4093 (1903).

[4] Colombano, *C.* **08**. i. 23.

[5] C. Smith, Mitchell, *J. C.S.* **1908**. 843.

The argument of Goldschmidt, that the ortho compounds are quinoid because they do not react with phenyl isocyanate, he has himself shown to be untenable,[1] as the reaction can be brought about under suitable conditions. Goldschmidt has therefore abandoned his former view, and now considers that all oxy-azo-compounds are true phenols.

An investigation of the ethers and esters (alkyl and acyl derivatives) of the oxy-azo-compounds by Auwers, Goldschmidt, Hewitt, Willstätter, and others, has shown that these bodies are all true phenol derivatives. In those cases where the acyl hydrazone compounds can be prepared, as by the action of asymmetrical phenyl-benzoyl-hydrazine on quinone, they change over with unexpected ease into the true azo-compounds[2]:—



This suggests that the free hydrogen compounds, which can change much more easily, will also assume the phenol structure.

Borsche[3] has examined the case of bodies containing the group

$$HO{\cdot}C_6H_4{\cdot}N{=}N-$$

attached to other than aryl radicals, and his results indicate that here also the azophenol structure is more stable than the isomeric quinone-hydrazone.

The evidence from the physical behaviour of the free oxy-azo-compounds, such as it is, points to the same conclusion, or at least does not contradict it. Auwers[4] showed that the cryoscopic behaviour of the para oxy-azo-compounds was that of phenols, while the ortho bodies gave ambiguous results. The evidence on which Hantzsch and Farmer[5] based the view that these bodies were pseudo-acids was weak, and they have subsequently abandoned it. But more recently Hantzsch and Glover[6] have shown, from the consideration of their colour, that the free para compounds must have the same constitution as their ethers and esters, i. e. that they must be phenols. Lemoult[7] concludes from the heat of combustion of a series of azo-dyes that they are all true azo-compounds. Tuck[8] claims to have proved from the ultra-violet absorption that all the para derivatives are of the phenol type, and also the ether of the ortho series; but that the free ortho compounds and their acyl derivatives are hydrazones. Not only, however, is the whole basis of his method open to some doubt, but the actual results point just as much in the opposite direction.

We may conclude, therefore, that the free oxy-azo-compounds, whether they belong to the ortho or to the para series, have the true phenol structure

$$Ar{\cdot}N{=}N{\cdot}C_6H_4{\cdot}OH.$$

This is an example of the general tendency of the quinoid derivatives (and the hydroaromatic bodies in general) to pass back if possible into aromatic com-

[1] Goldschmidt, Löw-Beer, *Ber.* **38.** 1098 (1905).

[2] Willstätter, Veraguth, *Ber.* **40.** 1432 (1907).

[3] *Ann.* **334.** 143 (1904); Borsche, Ockinga, ib. **340.** 85 (1905); Borsche, ib. **343.** 176 (1905); **357.** 171 (1907).

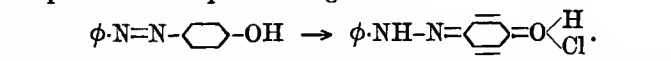
[4] Auwers, Orton, *Z. Ph. Ch.* **21.** 355 (1896); Auwers, *Ber.* **33.** 1302 (1900).

[5] Hantzsch, *Ber.* **32.** 590; Hantzsch, Farmer, ib. 3089 (1899).

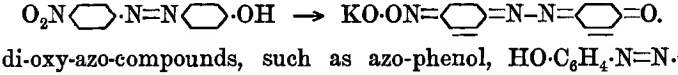
[6] *Ber.* **39.** 4153 (1906). [7] *C. R.* **143.** 603 (1906). [8] *J. C. S.* **1907.** 449.

pounds. (Compare the case of the quinols.) When the passage of the azo into the hydrazone type does not involve the production of a quinoid ring (as in the mixed azo-compounds), the hydrazone structure is the more stable, as is shown by the ease with which benzene-azo-methane goes over into acetaldehyde phenyl-hydrazone.

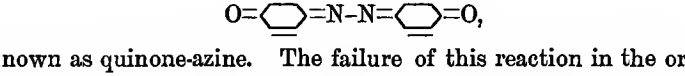
The alkaline salts may be taken to have the same constitution as the mother substances, for it is scarcely likely that the replacement of the hydrogen by a metal will favour the hydrazone as opposed to the phenol form. On the other hand the oxy-azo-compounds can also act as very weak bases and form salts with acids. This salt formation produces a difference in colour, but Tuck[1] has shown that the same difference is produced in the free oxy-azo-compound as in its ethyl ether. This excludes the possibility of its going over into a hydrazone. Fox and Hewitt[2] have found that while *p*-oxy-azobenzene gives with dilute nitric acid (which does not produce the salt to any great extent) the ortho-nitro derivative, if it is nitrated in concentrated sulphuric acid solution, where it is present practically entirely as the salt, the nitro-group goes into the para position. This shows that the formation of the salt involves some change of structure, as might be expected from the change of colour, while it must be a change which can occur with the alkyl derivative. They therefore suggest that the salt is an oxonium compound with a quinoid ring:—



Hewitt and Mitchell[3] point out that both in the oxy- and in the aminoazo-compounds, the introduction of a nitro-group in the para position to the azo results in a compound which changes colour and becomes bluer on treatment with alkali. This indicates a change of constitution, due to the presence of the nitro-group, and on the analogy of the nitrophenols we may assume in this case the production of the quinoid form:—



The di-oxy-azo-compounds, such as azo-phenol, $HO{\cdot}C_6H_4{\cdot}N{=}N{\cdot}C_6H_4{\cdot}OH$, present certain remarkable peculiarities.[4] Para-azo-phenol (but not the meta or ortho compounds, nor the corresponding amino-derivatives) can be oxidized by silver oxide or lead dioxide to a substance which must have the formula



and is known as quinone-azine. The failure of this reaction in the ortho series is a strong argument against the ortho oxy-azo-compounds having a quinoid structure, as in that case they ought to oxidize easily. Quinone-azine occurs in two different solid forms, which are possibly stereoisomers. On reduction it takes up two atoms of hydrogen again, but the product is not the original azo-phenol but a new modification. The differences between the two forms of azo-phenol are small, but quite distinct (in colour, solubility, &c.). The isomerism is maintained in solution and in the salts. The fact that neither form is reduced further by such agents as phenyl-hydrazine indicates that neither of them

[1] l. c. [2] *J. C. S.* **1908**. 333. [3] *J. C. S.* **1907**. 1251.
[4] Willstätter, Benz, *Ber.* **39**. 3482, 3492 (1906); **40**. 1578 (1907).

possesses a quinoid structure. This is further proved by the fact that they give two di-ammonium salts (which cannot be derived from a quinoid form) which regenerate the original α- and β-azo-phenol with acids. This seems to exclude structural isomerism, and to make it certain that they are stereoisomers. There are other cases in which stereoisomerism among azo-compounds is suspected,[1] though in none has it been definitely established. A more detailed investigation of the two para-azo-phenols shows that each of the two forms is capable of existing in two modifications, each pair changing more readily into one another than into the other pair; and the difference persists even in the acetyl derivatives. No explanation has been offered of this.

AZOXY-COMPOUNDS

These bodies, which have the general structure

$$\mathrm{Ar{\cdot}N\!\!<\!\!\begin{matrix}\\ O\end{matrix}\!\!>\!\!N{\cdot}Ar},$$

are the first bimolecular reduction-products of the aromatic nitro-compounds. They are made by boiling the nitro-bodies with alcoholic potash. The real reducing agent is the alcohol, which is oxidized to the corresponding acid. In this reaction it is found that ethyl is more powerful than methyl alcohol, and potash than soda.

This method cannot be used if there is a methyl group in the para position to the NO_2, as in that case some of the hydrogen required for the reduction is taken from the methyl, and a dibenzyl or stilbene derivative is formed. It is also possible to reduce the alcoholic solution of the nitro-body with sodium amalgam, or to use zinc dust in the presence of alcoholic ammonia.

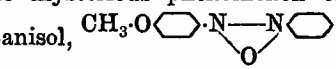
The azoxy-compounds are likewise formed by the oxidation of azo- and hydrazo-compounds, and, as we have seen, by the action of nitroso-compounds on β-aryl-hydroxylamines. This last method of formation is of the utmost importance, since it is practically the sole source of the bimolecular reduction-products of the aromatic nitro-compounds.

The azoxy-compounds are crystalline bodies of low melting-point, and of a rather pale yellow colour. They cannot be distilled unchanged, and are converted into the azo-bodies by distillation with iron filings. One of their most interesting reactions is that when gently warmed with sulphuric acid many of them are converted into the isomeric oxy-azo-compounds (Wallach).

They have not been investigated in very great detail, and there is even some doubt as to their structure. But the only alternative to the usually accepted formula is $\mathrm{Ar{\cdot}N{=}\overset{\displaystyle O}{\overset{\|}{N}}{\cdot}Ar}$, which represents them as to some extent similar to the nitrosamines, $\mathrm{Ar{\cdot}\overset{\displaystyle N:O}{\overset{|}{N}}{\cdot}Ar}$; and it has been shown by Lachman that they differ from the nitrosamines in every possible way, being very inactive, while the nitrosamines are excessively active. So we may take the usual formula as sufficiently established.

[1] Cf. Jacobson, Hönigsberger, *Ber.* **36.** 4093, 4123, note 1 (1903).

Reissert[1] has obtained isomeric forms of azoxybenzene and of *o*-azoxytoluene. They are nearly colourless, even in solution, and have higher melting-points than the normal forms, into which they readily pass on warming or in presence of catalytic agents, such as bromine. They show no definite differences from the normal forms in chemical behaviour. Reissert suggests that they may have the structure $\begin{matrix} Ar\cdot N \\ \| \\ O \end{matrix}=N\cdot Ar$.

The most remarkable point about the azoxy-compounds is that in a certain number of them the mysterious phenomenon of liquid crystals has been observed. If *p*-azoxy-anisol,  , is heated, it melts at 116° to a turbid liquid, which at 134° suddenly becomes clear. The clear liquid is perfectly normal in its behaviour, and like other liquids. The turbid liquid is found to possess strong double refracting power. This would seem to imply that the orientation of the molecules which exists in the (solid) crystal is maintained in the liquid. Various theories have been advanced to explain away the phenomenon, as that the turbid liquid is an emulsion of two liquid phases, or a suspension of small solid crystals in the liquid. But these have been disproved, and there can be no doubt that we are dealing with a real liquid, in which, nevertheless, the molecules are maintained in a certain fixed arrangement. The turbidity is merely due to the fact that the various crystal drops have their axes in different directions, and so resembles that of a mass of powdered crystals. The phenomenon is widely spread among certain classes of azoxy-derivatives, and is also observed in bodies of quite a different type, such as the cholesteryl esters. With some bodies the clearing temperature is below the melting, so that the liquid crystal phase can only be observed in the supercooled liquid. In certain compounds Vorländer has noticed the occurrence of two different liquid crystalline phases, one dark and the other light in colour, with a perfectly definite transition point. The most inexplicable point about the whole phenomenon is perhaps the fact that the viscosity of the crystalline liquid is in nearly all cases less (and sometimes much less) than that of the isotropic form.

NITROSAMINES

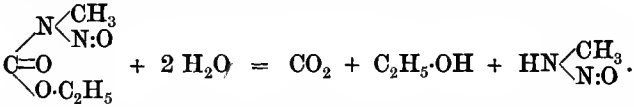
The nitrosamines are derived from the amines by replacing a hydrogen attached to nitrogen by NO. Hence two classes are theoretically possible, the primary R·NH·NO, and the secondary $R_2N\cdot NO$. Among the fatty compounds (other than the derivatives of carbonic acid) the primary nitrosamines do not exist at all. There are several reactions which might be expected to produce them, but they yield only their decomposition products. Thus a primary amine with nitrous acid might give either a primary nitrosamine or a diazo-compound:—

$$CH_3\cdot NH_2 + HO\cdot N{:}O = CH_3\cdot NH\cdot N{:}O + H_2O,$$
$$\text{or } CH_3\cdot NH_2 + O{:}N\cdot OH = CH_3\cdot N{=}N\cdot OH + H_2O.$$

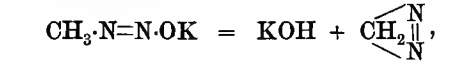
As a fact, of course, neither is obtained, but only nitrogen and the alcohol.

[1] *Ber.* **42.** 1364 (1909).

A reaction which gives a good illustration of the degree of stability of these primary nitrosamines is the saponification of nitroso-methyl-urethane. This would naturally lead to the formation of methyl nitrosamine :—



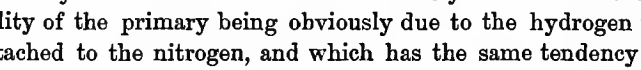
Hantzsch has shown that in the presence of excessively concentrated aqueous potash this will give a true diazotate, $CH_3{\cdot}N{=}N{\cdot}OK$, a tautomer of the expected nitrosamine, but this loses potash with the utmost ease, in fact almost explosively, to form diazomethane :—



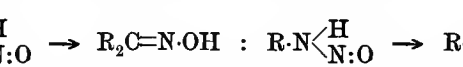
and the latter reacts with water to give nitrogen and methyl alcohol.

On the other hand, in the aromatic series, as we have seen, the primary nitrosamines can be isolated. They are formed by spontaneous change from the anti-diazo-hydrates. But even here they are very unstable, and can exist only in the solid state or in neutral solution. The presence of hydrogen or hydroxyl ions converts them either into a diazonium or into a diazo-compound. In fact these aromatic nitrosamines are at once pseudo-acids and pseudo-bases.

The secondary nitrosamines exist both in the fatty and in the aromatic series: the instability of the primary being obviously due to the hydrogen which still remains attached to the nitrogen, and which has the same tendency to go over to the oxygen which we observe in the simple primary or secondary nitroso-compounds :—

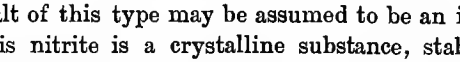


Secondary nitrosamines are formed by the action of nitrous acid on secondary amines :—



In one case, that of di-isopropylamine, the nitrite, $\begin{matrix}(CH_3)_2CH\\(CH_3)_2CH\end{matrix}\!\!>\!NH{\cdot}HNO_2$, can be isolated ; and a salt of this type may be assumed to be an intermediate product in all cases. This nitrite is a crystalline substance, stable in cold aqueous solution, and only goes slowly on boiling into the nitrosamine. In all other cases, even with normal dipropylamine, the nitrosamine is formed at once in the cold.

The fatty nitrosamines are also formed in a curious way, by heating the nitrates of the secondary amines to 150°, when they give off oxygen :—



The secondary nitrosamines are liquids or solids, volatile in steam. The fatty distil without change, but the aromatic do not. They are much used for isolating the secondary amines. They separate out as oils on treating the mixed bases with potassium nitrite and acid. They can be made to re-form the secondary amines, the fatty by heating with concentrated hydrochloric acid, the aromatic by reduction with tin and hydrochloric acid.

Weaker reducing agents, such as zinc and acetic acid in alcoholic solution, convert them into the secondary hydrazines such as $\begin{matrix}CH_3\\ \phi\end{matrix}\!\!>\!N\text{–}NH_2$. They give the Liebermann reaction for nitroso-compounds. This is effected by warming them with strong sulphuric acid and phenol, when a red colour is produced, which, on pouring the liquid into water and adding excess of alkali, turns to a beautiful blue.

When the mixed (fatty-aromatic) secondary nitrosamines are fused with potash, a part is decomposed into nitrous acid and the secondary amine, while another part splits between the nitrogen and the fatty radical, and gives phenyl-nitrosamine, which forms its potassium salt, the anti-diazotate.

If they are treated with alcoholic hydrochloric acid the nitroso-group migrates as usual to the ring, giving *p*-nitroso-methyl-aniline, $O{:}N\text{⬡}N\!<\!\begin{matrix}CH_3\\ H\end{matrix}$. The same effect is produced by alcoholic hydrobromic acid, but curiously not by alcoholic sulphuric acid.

NITRAMINES

The nitro-amines or nitramines are bodies in which one hydrogen atom of an NH_2 group is replaced by NO_2. They are more stable than the nitrosamines, as NO_2 is usually more stable than NO, and both the primary and the secondary compounds are known.

The primary fatty nitramines are formed from the monalkyl-urethanes or the monalkyl-oxamides. These bodies on treatment with anhydrous nitric acid are nitrated in the NH group thus:—

$$\begin{matrix}CH_3\cdot NH\\ |\\ CO\cdot OEt\end{matrix} \rightarrow \begin{matrix}CH_3\cdot N\cdot NO_2\\ |\\ CO\cdot OEt\end{matrix},$$

$$\begin{matrix}O{=}C\cdot NH\cdot Et\\ |\\ O{=}C\cdot NH\cdot Et\end{matrix} \rightarrow \begin{matrix}O{=}C\cdot N\!<\!\begin{matrix}NO_2\\ Et\end{matrix}\\ |\\ O{=}C\cdot N\!<\!\begin{matrix}Et\\ NO_2\end{matrix}\end{matrix}.$$

When the products are treated with ammonia, the nitramine group is replaced by the NH_2 of the ammonia, giving acetamide or oxamide and the ammonium salt of the nitramine, which we may write $CH_3\cdot NH\cdot NO_2\cdot NH_3$. This, when boiled with alkali, loses the ammonia and gives the free nitramine.

The primary alkyl nitramines are acid substances, which react with alkyl iodide and potash to form the dialkyl nitramines, such as $\begin{matrix}C_2H_5\\ CH_3\end{matrix}\!\!>\!N\cdot NO_2$.

The aromatic nitramines are the so-called diazobenzenic acid and its substitution-products. This body is got by oxidizing potassium diazobenzene, or better potassium isodiazobenzene, with potassium ferricyanide.[1] It is also produced by the action of nitrogen pentoxide on an ethereal solution of aniline at $-10°$, which is evidence for its being the true nitro-amine $\phi\cdot NH\cdot NO_2$. In the same way its alkyl derivatives can be made by the action of fuming nitric acid on the monalkyl- or (with the loss of an alkyl group) on the dialkyl-anilines.

[1] Bamberger, *Ber.* **27**. 915 (1894).

Phenyl nitramine melts at 46° and explodes at 100°. It is slightly soluble in water, giving an acid solution. It is very sensitive to acids, being converted mainly into ortho but partly into para nitraniline, a further proof of its constitution. This tendency of the nitro-group to migrate to the ring is of course the normal behaviour of a substituent attached to the nitrogen atom of aniline; and as usual the ortho and para positions are taken up, but under no conditions the meta, and the reaction is promoted by the presence of hydrogen ions. If the para and both the ortho positions are already occupied by halogen (in *s*-trichloro- and *s*-tribromo-phenyl nitramine) the nitro-group is able to turn out the para halogen atom, either expelling it from the compound altogether, or moving it on to the next carbon of the ring.[1]

Phenyl nitramine is very stable to alkali, and is not decomposed by it unless it is fused with potash at 230–260°, when it is converted into aniline and potassium nitrite and nitrate. On reduction in alkaline solution it gives first phenyl nitrosamine and then phenyl-hydrazine.

Its sodium salt reacts with methyl iodide to give phenyl-methyl nitramine, $\phi\overset{CH_3}{\diagdown}N\cdot NO_2$, which is converted by acids into ortho and para nitro-methylaniline, and reduces, like the mother substance, to phenyl-methyl nitrosamine and then to unsymmetrical phenyl-methyl-hydrazine: whereby its formula is established.

Its silver salt, when treated with methyl iodide, yields a very unstable isomer of this, which decomposes on standing, and is probably an oxygen ester.

As regards the constitution of these bodies, it is fairly certain that free phenyl nitramine has the structure $\phi\cdot NH\cdot NO_2$. This is supported by its formation from aniline and nitrogen pentoxide, and by its conversion into ortho and para nitraniline. It is, however, tautomeric in behaviour, and gives two series of ethers, one of which undoubtedly has the structure $\overset{Ar}{Alk}\diagdown N\cdot NO_2$, the bodies being true secondary nitramines. These must therefore be the derivatives of the normal form. On the other hand Hantzsch and Dollfus[2] have shown that it gives the ammonia reaction for pseudo-acids: that is, in dry benzene solution it combines with dry ammonia much more slowly than a true acid (like benzoic acid) does, which indicates that it requires to go over into the tautomeric form in order to form the salt. In aqueous solution, since it is a fairly strong acid (about as strong as acetic acid), it must be largely present in the isomeric hydroxyl form, from which the alkaline salts and no doubt the second series of ethers—the O-ethers—are derived. This form may probably be, on the analogy of the isonitro-compounds, $Ar.N{=}N\overset{O}{\diagdown}_{OH}$; but there is no direct proof of this, and it may conceivably be $Ar\cdot N\!\!-\!\!\!\!\begin{array}{l}\diagup N\cdot OH\\ \diagdown O\end{array}$, a formula which is in fact adopted by Scholl.[3]

[1] Orton, Smith, *J. C. S.* **1905**, 389; **1907**. 146.
[2] *Ber.* **35**. 259 (1902); Hantzsch, ib. **39**. 2103 (1906).
[3] *Ann.* **338**. 11 (1904).

NITRIMINES [1]

Certain ketoximes, especially those of the camphor series, when they are treated with nitrogen peroxide, instead of forming pseudonitrols in the normal manner, convert the oxime group into the group N_2O_2. This reaction seems to be confined to those compounds which have the C=NOH group attached on one or both sides to a tertiary or a doubly linked or a quaternary carbon atom. The products are known as nitrimines, and it is evident from their behaviour that they belong to the class of nitramines. They give the Liebermann reaction, the Thiele-Lachman reaction for nitramines (the formation with strong sulphuric acid of nitrous oxide and nitric acid), they can in some cases be reduced to hydrazines, and their behaviour with alkalies is that of the alkyl nitramines and other pseudo-acids. There can thus be no doubt that the characteristic group, $C_2HN_2O_2$, which they contain must be written either $>C=\overset{|}{C}\cdot NH\cdot NO_2$ or $>CH\cdot\overset{|}{C}=N\cdot NO_2$. It is a strong argument in favour of the second of these two structures that unlike the primary nitramines they will react neither with diazomethane nor with phenyl isocyanate.

They give two series of alkyl derivatives, one having the alkyl attached to nitrogen and the other to oxygen. The salts are obviously derived from the same form as the second series of ethers, and in many cases this second form, which must be $>C=\overset{|}{C}\cdot N=N\langle^{O}_{OH}$ or $>C=\overset{|}{C}\cdot N\!-\!\!-\!N\cdot OH$ (with the O bridging the two N), can actually be isolated.

The passage of the pseudo-acid form into the true acid form (e.g. in presence of an alkali) involves the formation of an intermediate compound:—

$$>CH\cdot\overset{|}{C}=N\cdot NO_2 \rightarrow >C=\overset{|}{C}\cdot NH\cdot NO_2 \rightarrow >C=\overset{|}{C}\cdot N=N\langle^{O}_{OH}.$$

The N-ethers are obviously derived from this intermediate compound.

In the nitrimine derived from chlorocamphor a remarkable case of intramolecular migration has been observed.[2] The nitro-group changes over spontaneously from the nitrogen to the next carbon atom, giving the free imine, which can easily be hydrolysed to the chloronitro-camphor:—

$C_8H_{14}\langle^{C=N\cdot NO_2}_{CHCl}$	$C_8H_{14}\langle^{C=NH}_{C\cdot Cl\cdot NO_2}$	$C_8H_{14}\langle^{C=O}_{CCl\cdot NO_2}$
Chlorocamphor-nitrimine.	Chloronitro-camphor-imine.	Chloronitro-camphor.

This change is exactly analogous to the transformation of phenyl nitramine into ortho-nitraniline; but among other than aromatic bodies such changes are rare.

ISONITRAMINES [3]

Isomeric with the nitramines are the so-called isonitramines, which are probably nitroso-hydroxylamines, $R\cdot N\langle^{OH}_{N:O}$. The fatty isonitramines are ob-

[1] Scholl, *Ann.* **338**. 1. (1905); **345**. 363 (1906).

[2] Angeli, Angelico, Castellana, *Atti Linc.* **12**. i. 428 (*C.* **03**. ii. 373).

[3] Traube, *Ber.* **29**. 1785 (1895); **29**. 667 (1896); Gomberg, *Ann.* **300**. 59 (1898).

tained by treating sodium acetoacetic ester with nitric oxide in the presence of sodium ethylate :—

$$\begin{matrix}CH_3\cdot CO\\EtO\cdot CO\end{matrix}\!\!>\!CNa_2 + 2\,NO = \begin{matrix}CH_3\cdot CO\\EtO\cdot CO\end{matrix}\!\!>\!C\!<\!\begin{matrix}N(ONa)\cdot N:O\\Na\end{matrix}.$$

When the product is hydrolysed by alkali, it gives the salt of isonitramine acetic acid, $\begin{matrix}CH_2\cdot N(OH)NO\\|\\CO\cdot OH\end{matrix}$.

With dilute mineral acids these bodies change over into the so-called amidoxyl-fatty acids, such as $\begin{matrix}CH_2\cdot NH\cdot OH\\|\\CO\cdot OH\end{matrix}$, which are β-hydroxylamine derivatives. On reduction in alkaline solution they give diazoacetic acid, no doubt through the intermediate production of the nitrosamine and the true diazo-compound :—

$$\begin{matrix}CH_2\cdot N(OH)NO\\|\\CO\cdot OH\end{matrix} \rightarrow \begin{matrix}CH_2\cdot NH\cdot NO\\|\\CO\cdot OH\end{matrix} \rightarrow \begin{matrix}CH_2\cdot N{=}N\cdot OH\\|\\CO\cdot OH\end{matrix} \rightarrow \begin{matrix}CH\!<\!\begin{matrix}N\\\|\\N\end{matrix}\\|\\CO\cdot OH\end{matrix}.$$

The aromatic isonitramines are obtained directly from the β-aryl-hydroxylamines by treatment with nitrous acid :—

$$\phi\cdot N\!<\!\begin{matrix}OH\\H\end{matrix} + HO\cdot NO = \phi\cdot N\!<\!\begin{matrix}OH\\NO\end{matrix} + H_2O.$$

The isonitramines are not pseudo-acids, and even in benzene solution give salts at once with ammonia. This shows that under all circumstances the molecule contains a hydroxyl group. They are, however, tautomeric, giving two series of esters ; but both of these have the alkyl attached to oxygen. One of these series is probably derived directly from the nitroso-hydroxylamine formula, which may therefore be assumed to be one of the tautomeric structures of the free isonitramines :—

$$R\cdot N\!<\!\begin{matrix}OCH_3\\N:O\end{matrix} \quad : \quad R\cdot N\!<\!\begin{matrix}OH\\N:O\end{matrix}.$$

The structure of the other form is unknown ; it may possibly be either $R\cdot N\!<\!\begin{matrix}O\\N\cdot OCH_3\end{matrix}$ or $R\cdot N\!<\!\begin{matrix}N\cdot OCH_3\\O\end{matrix}$, whichever of these two formulae is not to be assigned to the O-esters of the normal nitramines.

CHAPTER XIII

DERIVATIVES OF CARBONIC ACID

AMINO-URETHANE, or hydrazine carboxylic ester, $C{=}O(NH{\cdot}NH_2)(OEt)$, can be obtained by the reduction of nitro-urethane with zinc and acetic acid. A similar but more important body is amino-urea, $CO(NH{\cdot}NH_2)(NH_2)$, generally known as *semi-carbazide*. This is obtained in the same way, by the reduction of nitro-urea,

$$CO(NH{\cdot}NO_2)(NH_2).$$

It may also be got from hydrazine and cyanic acid :—

$$C{=}NH{=}O + \begin{matrix} H \\ | \\ HN{\cdot}NH_2 \end{matrix} = CO(NH_2)(NH{\cdot}NH_2).$$

It is a crystalline substance melting at 96°, and has basic properties, forming salts with one equivalent of acid. Its importance lies in the fact that it reacts very readily with aldehydes and ketones after the manner of phenyl-hydrazine, to give semicarbazones :—

$$CO(NH{\cdot}NH_2)(NH_2) + O{=}C(CH_3)(CH_3) = CO(NH{\cdot}N{=}C(CH_3)(CH_3))(NH_2) + H_2O.$$

These compounds usually crystallize well and are not over soluble, so that in many cases semicarbazide is better than phenyl-hydrazine for characterizing such carbonyl compounds.

It is remarkable that the monosemicarbazones of the α-diketones form deep yellow solutions in alkali, in which respect they resemble the monoximes of the α-diketones. It has been suggested[1] that this is due to their going over as pseudo-acids into an acidic enolic form :—

$$\begin{matrix} CH_3{\cdot}C{=}O \\ | \\ CH_3{\cdot}C{=}N{\cdot}NH{\cdot}CO{\cdot}NH_2 \end{matrix} \rightarrow \begin{matrix} CH_2{=}C{\cdot}OH \\ | \\ CH_3{\cdot}C{=}N{\cdot}NH{\cdot}CO{\cdot}NH_2 \end{matrix}.$$

This view is supported by the fact that the corresponding derivative of benzil,

$$\begin{matrix} \phi{\cdot}C{=}O \\ | \\ \phi{\cdot}C{=}N{\cdot}NH{\cdot}CO{\cdot}NH_2 \end{matrix},$$

which could not form such an enol, is the only body of this type which is insoluble in dilute alkali.

[1] Diels, van Dorp, *Ber.* **36**. 3183 (1903).

Thiosemicarbazide, $CS\begin{smallmatrix}\diagup NH\cdot NH_2\\ \diagdown NH_2\end{smallmatrix}$, is interesting from the fact that it forms two isomeric diphenyl derivatives. They are prepared by acting on phenyl-hydrazine with phenyl mustard oil, a reaction which one would expect to take place in this way:—

$$C\begin{smallmatrix}\diagup S\\ \diagdown N\cdot\phi\end{smallmatrix} + H_2N\cdot NH\cdot\phi = CS\begin{smallmatrix}\diagup NH\cdot NH\cdot\phi\\ \diagdown NH\cdot\phi\end{smallmatrix}.$$

If the reagents are heated, the stable or β-form is obtained. But at a low temperature an unstable isomer (the α-form) is produced. This changes very readily, even on recrystallization from alcohol, into the β modification. It might be supposed that the isomerism was due to one form having the normal structure (given above) and the other being the iso-compound, $C\begin{smallmatrix}=N\cdot NH\cdot\phi\\ \diagdown SH\\ \diagdown NH\cdot\phi\end{smallmatrix}$.

But it has been shown by Marckwald[1] that both forms contain an SH group, since they both react with methyl iodide to give an ether which has the methyl group attached to sulphur. There thus remain only two possible explanations: either that they are structural isomers with the formulae:—

$C\begin{smallmatrix}=N\cdot NH\cdot\phi\\ \diagdown SH\\ \diagdown NH\cdot\phi\end{smallmatrix}$ and $C\begin{smallmatrix}\diagup H_2N\cdot N\cdot\phi\\ \diagdown SH\\ =N\phi\end{smallmatrix}$,

or that they are stereoisomers:—

$HS\cdot C\begin{smallmatrix}\cdot NH\phi\\ \| \\ N\cdot NH\cdot\phi\end{smallmatrix}$ and $HS\cdot C\begin{smallmatrix}\cdot NH\cdot\phi\\ \| \\ \phi\cdot NH\cdot N\end{smallmatrix}$.

Marckwald decided against the first of these theories, mainly on the ground that so great a change of structure could not occur so easily. He therefore concluded that the bodies were stereoisomers. Recently, however, it has been shown[2] that the first explanation (that of structural isomerism) is undoubtedly the true one. The substance formed by the action of phenyl-hydrazine on phenyl mustard oil at a low temperature (the unstable form) has the structure $HS\cdot C\begin{smallmatrix}=N\cdot\phi\\ |\\ \phi\cdot N\cdot NH_2\end{smallmatrix}$, while the stable form is $HS\cdot C\begin{smallmatrix}=N\cdot\phi\\ |\\ NH\cdot NH\cdot\phi\end{smallmatrix}$ or possibly $HS\cdot C\begin{smallmatrix}\cdot NH\cdot\phi\\ \| \\ N\cdot NH\cdot\phi\end{smallmatrix}$.

The case is of considerable interest from the remarkable ease with which the mustard oil residue migrates from the α- to the β-nitrogen atom of the phenyl-hydrazine.

Both amino-urethane, which has already been mentioned, and amino-guanidine, $C\begin{smallmatrix}\diagup NH\cdot NH_2\\ =NH\\ \diagdown NH_2\end{smallmatrix}$, which is obtained by the reduction of nitro-guanidine, and is used for preparing hydrazine, react with carbonyl compounds in the same way as semicarbazide. In fact this reaction is common to all bodies of the type $H_2N\cdot R$, where R is a more or less negative group (OH, $NH\phi$, or a modified urea residue).

[1] *Ber.* **25.** 3098 (1892); cf. Hantzsch, *Ber.* **26.** 16; V. Meyer, ib. 17 (1893).

[2] Busch, Holzmann, *Ber.* **34.** 320 (1901).

All the bodies so far considered are of course hydrazine derivatives. We might expect to get a corresponding series of derivatives of diimide, NH=NH. This substance is itself unknown: indeed it seems to be incapable of existence, since several reactions are known which ought to produce it, but in none of them is it formed. It appears to break up as soon as it is produced, usually into hydrazine and nitrogen:—

$$\begin{matrix} HN{=}NH \\ + \\ HN{=}NH \end{matrix} \quad = \quad \begin{matrix} H_2N{-}NH_2 \\ + \\ N{\equiv}N \end{matrix} .$$

In the same way the mono-derivatives of diimide cannot be prepared. It is necessary that both hydrogen atoms should be replaced before a compound is formed sufficiently stable to be isolated.

Derivatives in which the N=N group is attached only on one side to carbon we have already met with in the true aromatic diazo-compounds. Another class of bodies of this kind is found among the nitroso-derivatives of the amides of carbonic acid, the desmotropic form of –NH·NO being –N=N·OH. But there are also some true azo-bodies among the carbonic acid derivatives, which have the N=N group linked to carbon on both sides. These are the derivatives of azo-dicarboxylic acid, $CO_2H{\cdot}N{=}N{\cdot}CO_2H$. They are made in two ways.

1. If hydrazine is treated with a solution of a cyanate, the hydrazine cyanate first produced changes into hydrazo-dicarboxyl-amide, just as ammonium cyanate changes into urea:—

$$\begin{matrix} NH_3{\cdot}N{=}C{=}O \\ | \\ NH_3{\cdot}N{=}C{=}O \end{matrix} \quad = \quad \begin{matrix} NH{\cdot}CO{\cdot}NH_2 \\ | \\ NH{\cdot}CO{\cdot}NH_2 \end{matrix} ,$$

as:—

$$NH_4{\cdot}N{=}C{=}O \quad = \quad NH_2{\cdot}CO{\cdot}NH_2,$$

and when this is treated with chromic acid, the two hydrogen atoms of the hydrazo-group are oxidized off, and azo-dicarboxylamide, $\begin{matrix} N{\cdot}CO{\cdot}NH_2 \\ \| \\ N{\cdot}CO{\cdot}NH_2 \end{matrix}$, is formed.

2. The second method is to oxidize amino-guanidine with nitric acid. The hydrazine NH_2 groups are oxidized off along with the hydrogen atom from the next NH, and the two residues unite:—

$$\begin{matrix} H_2N{\cdot}C{\cdot}NH{\cdot}NH_2 \\ \| \\ NH \end{matrix} + \begin{matrix} H_2N{\cdot}NH{\cdot}C{\cdot}NH_2 \\ \| \\ NH \end{matrix} + 3\,O \; = \; \begin{matrix} H_2N{\cdot}C{\cdot}N{=}N{\cdot}C{\cdot}NH_2 \\ \| \quad\quad \| \\ NH \quad\quad NH \end{matrix} + 3\,H_2O + N_2.$$

This gives the amidine of azo-dicarboxylic acid, which like all amidines exchanges its NH for oxygen on saponification (boiling with water), to form azo-dicarboxyl-amide. This is an orange-red powder (the usual azo colour), and on treatment with concentrated potash gives the potassium salt of the corresponding azo-dicarboxylic acid, $\begin{matrix} N{\cdot}CO{\cdot}OK \\ \| \\ N{\cdot}CO{\cdot}OK \end{matrix}$, a very unstable salt, which readily splits up into carbon dioxide, nitrogen, and hydrazine. Many attempts have been made to isolate diimide from this compound, a reaction which one would expect from analogy to go easily, but they have all failed.

Nitroso-derivatives of the amides of carbonic acid

In the case of the secondary compounds (the alkyl derivatives) these can be formed by the direct action of nitrous acid; in the case of the primary amides, such as urethane itself, the nitroso-derivatives are formed by the reduction of the nitro-compounds.

The behaviour of the two classes of derivatives, the primary and the secondary, is very different.

Of the primary, nitrosourethane is almost the only representative. It is obtained by reducing the ammonium salt of nitrourethane with zinc and acetic acid, a reaction which may be written:—

$$\begin{matrix} NH\cdot NO_2 \\ CO \\ O\cdot Et \end{matrix} + 2\,H = \begin{matrix} NH\cdot NO \\ CO \\ O\cdot Et \end{matrix} + H_2O.$$

This body, ethyl nitrosocarbamate (not to be confused with nitroso-ethylurethane), is a crystalline compound melting at 51°, which readily decomposes, the course of its decomposition being somewhat remarkable.

With alkalies it breaks up into carbon dioxide, nitrogen, and alcohol:—

$$\begin{matrix} NH\cdot NO \\ CO \\ O\cdot C_2H_5 \end{matrix} = CO_2 + N_2 + C_2H_5\cdot OH,$$

whereas with acids only half the alcohol appears as such, the other half being broken up into ethylene and water:—

$$2\begin{matrix} NH\cdot NO \\ CO \\ O\cdot C_2H_5 \end{matrix} = 2\,CO_2 + 2\,N_2 + C_2H_5\cdot OH + C_2H_4 + H_2O.$$

The methyl compound, $\begin{matrix} NH\cdot NO \\ CO \\ O\cdot CH_3 \end{matrix}$, is similar, but even more unstable. On decomposition with sulphuric acid it does not form any hydrocarbon, but only methyl alcohol and traces of methyl sulphuric acid.

The structure ascribed to these bodies above is that which was originally assigned to them. But it has been shown by Hantzsch[1] that this does not correctly represent their constitution. There are two classes of compounds containing the group $-N_2OH$, the nitrosourethanes and the diazo-hydrates. Both these classes give highly ionized salts, which must be derived from the most negative of the two possible desmotropic formulae, the potassium salt, for instance, being R·N=N·OK and not R·NK·NO. The possibility of their having this form is shown by the fact that the silver salt of nitrosourethane forms an O-ether with ethyl iodide.

In the case of the diazo-hydrates, as we have seen, the hydrogen compounds of the strongly acidic form Ar·N=N·OH can be isolated, but are very unstable; and the only stable form is the tautomeric nitrosamine Ar·NH·NO.

But, curiously, the behaviour of the nitrosourethanes is the reverse of this. Here the free hydrogen compound, instead of being a neutral non-electrolyte, as

[1] *Ber.* **32.** 1703 (1899).

a nitrosamine would be, is always an electrolyte of strongly acid reaction, whose affinity constant can be measured, and which combines with dry ammonia even in benzene solution. These bodies must therefore have a constitution corresponding to that of their salts, and must really be diazo-urethane hydrates, $CO\begin{cases}N{=}N{\cdot}OH\\O{\cdot}Alk\end{cases}$. This view accords with their decomposition, in which, as in the normal decomposition of the diazo-compounds, nitrogen is evolved.

Hantzsch's results are in striking contradiction to the views previously held as to the constitution of these bodies. We have been accustomed to regard the free diazo-hydrates as true diazo-compounds, and the urethane derivatives as nitrosamines. But his work shows conclusively that the reverse is the case. The free iso-diazo-hydrates have at best only a temporary existence, the stable form being the nitrosamine, while the nitrosourethanes are really diazo-hydrates.

The secondary nitrosourethanes are obtained by the action of nitrous acid on the alkyl-urethanes:—

$$\begin{matrix}N\begin{cases}CH_3\\H\end{cases}\\C{=}O\\O{\cdot}Et\end{matrix} + HONO = \begin{matrix}N\begin{cases}CH_3\\NO\end{cases}\\C{=}O\\O{\cdot}Et\end{matrix} + H_2O.$$

The desmotropic diazo-formula is here excluded, since the mobile hydrogen is replaced by alkyl.

This body, nitroso-methyl-urethane, is chiefly remarkable as the source from which v. Pechmann first prepared diazomethane, a reaction which has already been discussed.

Of the nitroso-derivatives of urea only the secondary are known. The reduction of nitro-urea itself cannot be stopped at the stage of nitrosourea, but proceeds further to amino-urea or semicarbazide.

The secondary compounds are obtained in the usual manner from alkyl ureas and nitrous acid. On reduction they yield the amino-ureas or alkyl-semicarbazides, which are hydrolysed by alkalies to give the alkyl-hydrazines:—

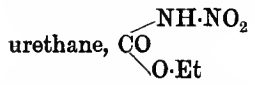
$$\begin{matrix}N\begin{cases}CH_3\\H\end{cases}\\C{=}O\\NH_2\end{matrix} \rightarrow \begin{matrix}N\begin{cases}CH_3\\NO\end{cases}\\C{=}O\\NH_2\end{matrix} \rightarrow \begin{matrix}N\begin{cases}CH_3\\NH_2\end{cases}\\C{=}O\\NH_2\end{matrix} \rightarrow \begin{matrix}CH_3{\cdot}NH{\cdot}NH_2\\+\ CO_2\\+\ NH_3\end{matrix}.$$

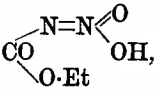
Nitroso-guanidine, $C\begin{cases}NH{\cdot}NO\\NH\\NH_2\end{cases}$, is prepared by reducing nitro-guanidine with zinc and sulphuric acid. It is a yellow powder which explodes without melting at 160°. It forms metallic salts of the usual anti-diazo type, but seems in the free state to be a true nitrosamine and not a diazo-hydrate. Thus it is neutral to litmus and is not an electrolyte. This view is supported by the fact that on decomposition it gives almost a quantitative yield of nitrous acid, and scarcely any nitrogen.

Nitro-derivatives

The nitro-derivatives of the amides of carbonic acid are obtained by direct nitration. For this purpose it is necessary, as in the aromatic series, to

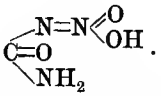
employ concentrated nitric acid in the presence of excess of strong sulphuric acid. In some cases the nitro-compounds are decomposed further by excess of nitric acid, and so only the theoretical quantity must be employed. This is most conveniently done by using the nitrate of the amide, which necessarily contains one equivalent of nitric acid, and adding this to excess of strong sulphuric acid, or, in some cases, of acetic anhydride. Nitro-



urethane, or  , is made in this way. It is a crystal-

line body melting at 64°, which has an acid reaction and forms salts. From its acid character it is fairly certain that it must in the free state be an iso-nitro-compound. On reduction it gives first nitroso- and then amino-urethane.

Nitro-urea, obtained by dissolving urea nitrate in strong sulphuric acid at a low temperature, is a crystalline compound which, when dry, is remarkably stable, and does not melt or decompose unless strongly heated; but in water it breaks up if heated above 60°. It is a strong acid, expelling acetic acid from its salts, and forms salts of neutral reaction. Hence it must be the iso-nitro-compound:—



Nitro-guanidine, which is prepared in the same way, is a substance of similar properties.

CHAPTER XIV

COMPOUNDS CONTAINING A CHAIN OF THREE OR MORE NITROGEN ATOMS

These bodies have been classified by Curtius, on the analogy of the carbon compounds, as derivatives of (mainly hypothetical) compounds of nitrogen and hydrogen corresponding to the hydrocarbons. Thus we have:—

NH_3, Ammonia, analogous to CH_4.

$NH_2{\cdot}NH_2$, Hydrazine, analogous to $CH_3{\cdot}CH_3$.

$NH_2{\cdot}NH{\cdot}NH_2$, Prozane, analogous to $CH_3{\cdot}CH_2{\cdot}CH_3$, propane.

$NH_2{\cdot}NH{\cdot}NH{\cdot}NH_2$, Buzane, analogous to $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$, butane,

and so forth. This nomenclature, though it is systematic, has not been much used, as nitrogen chains are much less stable than carbon chains, and therefore form a less satisfactory basis of classification.

DIAZOAMINO-COMPOUNDS

Of the three-nitrogen compounds the most important are the derivatives of prozene, $NH_2{\cdot}N{=}NH$, which may be regarded as the amidine of nitrous acid. To this class belong the diazoamino-compounds, which, in the aromatic series, have long been known. They are readily formed by the action of aromatic diazo-compounds on aromatic (and in some cases fatty) amines in neutral or acetic acid solution, and are of course intermediate products in the formation of the aminoazo-dyes:—

$$Ar{\cdot}N{=}N{\cdot}OH + H_2N{\cdot}Ar = Ar{\cdot}N{=}N{\cdot}NH{\cdot}Ar + H_2O.$$

This method of formation can be modified in various ways. Solid diazobenzene chloride and normal potassium benzene-diazotate will combine with amines in the absence of water. The symmetrical derivatives can also be got directly by the action of one molecule of nitrous acid on two molecules of an aromatic amine. Another reaction which leads to them is that of the nitroso-anilides on the primary amines:—

$$\begin{matrix}\phi{\cdot}N{\cdot}N{=}O\\ |\\ CO{\cdot}CH_3\end{matrix} + H_2N{\cdot}\phi = \phi{\cdot}NH{\cdot}N{=}N{\cdot}\phi + CH_3{\cdot}CO{\cdot}OH.$$

The method of preparation through the diazo-compounds can of course only give derivatives containing at least one aromatic nucleus. But a general method of preparation is afforded by the action of an azide on an organo-magnesium compound[1]:—

$$R{\cdot}N\begin{matrix}N\\ \|\\ N\end{matrix} + R_1{\cdot}MgBr = \begin{matrix}MgBr\\ |\\ R{\cdot}N{-}N{=}N{\cdot}R_1\end{matrix} \longrightarrow R{\cdot}NH{\cdot}N{=}N{\cdot}R_1 + MgBrOH.$$

[1] Dimroth, *Ber.* **36**. 909 (1903).

By means of this reaction Dimroth [1] has succeeded in preparing the previously unknown diazoamino-paraffins, including the mother substance of the group, diazoamino-methane $CH_3{\cdot}NH{\cdot}N{=}N{\cdot}CH_3$, or, as it is more conveniently named, dimethyl-triazene. It is made by the action of methyl azide $CH_3{\cdot}N_3$ on methyl magnesium iodide. It is very difficult to isolate, being decomposed at once by all acids, even carbonic, and being also miscible with water and volatile even with ether vapour. It was obtained from the ethereal solution in the form of its cuprous compound $CH_3{\cdot}NCu{\cdot}N{=}N{\cdot}CH_3$. Acids cannot be used to decompose this compound, as they destroy the triazene, and it was therefore mixed with an equivalent of diazoamino-benzene, which is more acidic, and therefore takes up the copper, and the dimethyl-triazene was distilled over under reduced pressure. It is a colourless liquid, which solidifies on cooling to crystals which melt at $-12°$. It boils with slight decomposition at 92°, and explodes when suddenly heated. In spite of its power of forming salts with metals, its aqueous solution has an alkaline reaction, but it does not form salts with acids, as they decompose it at once ; even water containing carbon dioxide immediately breaks it up, two-thirds of the nitrogen being evolved, and methyl alcohol and methylamine produced :—

$$CH_3{\cdot}NH{\cdot}N{=}N{\cdot}CH_3 + H_2O = CH_3{\cdot}NH_2 + N_2 + CH_3OH.$$

In pure water it is fairly stable, but on addition of colloidal platinum nitrogen is evolved.

In the same way Dimroth [2] has prepared benzyl-methyl-triazene

$$\phi{\cdot}CH_2{\cdot}N_3H{\cdot}CH_3,$$

a liquid which is very unstable to acids, and a series of mixed derivatives, such as methyl-phenyl-triazene (M.Pt. 37°), and others, which are intermediate in properties between the purely fatty and the purely aromatic compounds. As the alkyl groups are replaced successively by aromatic radicals, the stability of the compound, especially to acids, increases, the aryl-triazenes being very fairly stable. At the same time the colour, both of the free triazenes and of their metallic derivatives, increases, as is shown by the following table :—

	Triazene.	*Silver salt.*	*Cuprous salt.*
Dimethyl-	Colourless	Colourless	Pale yellow
Methyl-benzyl- . .	Colourless	Colourless	Pale yellow
Phenyl-methyl- . .	Colourless	Yellow	Orange
Diphenyl-	Yellow-brown	Red	Brick red

Dimroth [3] has shown that the mixed derivatives can be made by treating the diazo-salts with the alkylamines ; but only under special conditions, as even traces of acid break up the triazene, while if the amine is not in excess the bis-diazoamino-compound $(Ar{\cdot}N{=}N{-})_2N{\cdot}Alk$ is formed.

The aromatic triazenes or diazoamino-compounds, which are much better known, are crystalline substances, insoluble in water, acids, and alkalies. They are generally yellow or brown, but in some cases the colour has been found to be due to an impurity : thus diazoamino-toluene, if carefully purified, is colourless.

[1] *Ber.* **39**. 3905 (1906). [2] *Ber.* **38**. 670 (1905).
[3] *Ber.* **38**. 2328 (1905).

They are feebly basic, forming unstable compounds with platinic chloride and unstable salts with strong acids. As in the fatty compounds the imide hydrogen can be replaced by metals, giving salts of the type Ar·N=N·NM·Ar. The mercury, copper, and silver salts are much more stable than those of the alkalies, as we should expect from the metal being attached to nitrogen.

Their behaviour in many respects is that of diazo-anilides. They easily split up into an amine and a diazo-compound or its decomposition-products. Thus in ethereal solution they are broken up by hydrobromic acid into the diazonium bromide and aniline hydrobromide. Cold concentrated hydrochloric acid converts diazoamino-benzene into aniline hydrochloride and chlorobenzene.

On reduction they give aniline and phenyl-hydrazine. All attempts to obtain as an intermediate reduction-product the prozane or triazane derivative

$$\text{Ar·NH·NH·NH·Ar},$$

hydrazoamino-benzene, have failed; although, as we shall see later, they have to a certain extent succeeded with some of the fatty derivatives.

When boiled with dilute hydrochloric acid they give phenol, nitrogen, and aniline, though they are often only slowly decomposed.

In all these reactions they behave as diazo-compounds, from which, however, they are distinguished by their much greater stability. Thus on heating they usually melt without decomposition at a fairly high temperature (diazoamino-benzene at 98°), and though on further heating they ultimately explode, yet they do so with much less violence than the diazo-compounds. Indeed by mixing them with sand, or by dissolving them in solvents of high boiling-point, such as aniline or liquid paraffin, this decomposition may be made to go quite quietly. It is then found that two-thirds of the total nitrogen is evolved as such, while the residue mainly consists (in the case of diazoamino-benzene) of ortho and para-amino-diphenyl.

The most important reaction of the diazoamino-bodies is their conversion into the aminoazo-compounds, which has already been discussed. This reaction is greatly assisted by the presence of an amine salt. Its velocity has been investigated by Goldschmidt and Reinders,[1] who dissolved in the amine known quantities of the salt and of the diazoamino-compound, and determined the amount of the latter which remained unchanged after a given time by measuring the volume of nitrogen evolved on heating it with acid. They found that the rate of formation of the aminoazo-compound was proportional to the quantity of diazoamino-body present (monomolecular), and also to the amount of amine salt. If different acids were used, the velocity was proportional to the strength of the acid. Where the ortho-aminoazo-compound is formed (owing to the para position being occupied) the reaction is much slower.

The structure of the diazoamino-compounds obviously admits of the same stereoisomerism as is observed among the simpler diazo-compounds. They may either be syn- or anti-bodies, $\begin{matrix}\text{Ar·N}\\ \|\\ \text{Ar·NH·N}\end{matrix}$ or $\begin{matrix}\text{Ar·N}\\ \|\\ \text{N·NH·Ar}\end{matrix}$. Their comparatively great stability, the absence of explosiveness, and the slowness with which they

[1] *Ber.* **29.** 1369, 1899 (1896); Goldschmidt, Merz, *Ber.* **30.** 670 (1897). For the influence of substituents on the formation of aminoazo-compounds see Morgan, Wootton, *J. C. S.* **1905.** 935.

couple, all show that they must have the anti-formula. Orlow[1] claims to have prepared an unstable isomer of diazoamino-benzene, which is more reactive than the normal form. This may possibly be the syn-compound, but its existence is doubtful.

There is another interesting question as to the structure of these bodies. The unsymmetrical diazoamino-compounds, i.e. those containing two different aromatic groups, exhibit a peculiar tautomerism. By condensing diazobenzene with toluidine we should expect to get the reaction :—

$$\phi\cdot N{=}N\cdot OH + H_2N\cdot C_7H_7 = \phi\cdot N{=}N\cdot NH\cdot C_7H_7 + H_2O,$$

and from diazo-toluene and aniline :—

$$C_7H_7\cdot N{=}N\cdot OH + H_2N\cdot\phi = C_7H_7\cdot N{=}N\cdot NH\cdot\phi + H_2O.$$

The two compounds with these formulae would be different, but they would be desmotropic, that is, they would differ only in the position of a hydrogen atom, and in the consequent position of the double bond.

As a fact the product obtained in both these reactions is the same. Moreover, the investigation of its behaviour for a long time led to no results capable of determining which of the two formulae it possesses. For example, on heating it with dilute hydrochloric acid we should expect that (as with the symmetrical compounds) the radical next to the NH would separate as amine, and the other as phenol. But the actual products are all the four possible substances: aniline and cresol, and toluidine and phenol.

It has, however, been shown by Dimroth that if the decomposition by acids is carried out at 0°, the reaction only goes in one direction, and only a single amine is formed. Now the structure of these bodies can be investigated in another way, which is due to Goldschmidt. They combine with phenyl isocyanate to form a diazo-urea :—

$$\begin{array}{l} Ar\cdot N{=}N\cdot NH\cdot Ar_1 \\ \quad + \quad OC{=}N\cdot\phi \end{array} = \begin{array}{l} Ar\cdot N{=}N\cdot N\cdot Ar_1 \\ \qquad\quad | \\ \qquad C{=}O \\ \qquad\quad | \\ \qquad NH\cdot\phi \end{array} \rightarrow \begin{array}{l} \qquad\quad NH\cdot Ar_1 \\ \qquad C{=}O \\ \qquad\quad NH\cdot\phi \end{array} + Ar\cdot OH + N_2 \quad ;$$

and this decomposes, splitting off the diazo-group, and leaving a simple di-substituted urea. The constitution of this last body may fairly be assumed to indicate the position of the hydrogen in the original diazoamino-compound. The aryl group which was joined to the imide nitrogen in the original compound will be that which remains in the resulting urea, while the one which was next to the diazo-group will be split off. Goldschmidt has applied this method to a large number of diazoamino-compounds with various substituents in the benzene ring, and finds that the imide group is always next to the most positive radical. Dimroth[2] has extended it to his mixed fatty-aromatic derivatives with a similar result, the imide group being always next to the alkyl radical. Thus, for example, from their behaviour with phenyl isocyanate we should conclude that benzene-diazoamino-toluene is $\phi\cdot N{=}N\cdot NH\cdot C_7H_7$, and the phenyl-methyl compound $\phi\cdot N{=}N\cdot NH\cdot CH_3$. Acetyl chloride behaves in the same way, giving a diazo-urea of the same type.

The remarkable point is that the results obtained by this method are

[1] *C.* **oe.** ii. 1569. [2] Dimroth, Eble, Gruhl, *Ber.* **40.** 2390 (1907).

diametrically opposed to those obtained by decomposing the bodies with acids. If methyl-phenyl-triazene is $\phi\cdot N{=}N\cdot NH\cdot CH_3$, we should expect that with acids at 0° it would give diazobenzene and methylamine. But it forms methyl alcohol (or methyl chloride), nitrogen, and aniline, not even a trace of a diazo-compound being produced. A certain amount of light is thrown on this question by the behaviour of the bis-diazoamino-compounds. These bodies are formed by the action of two molecules of the diazo-salt on one of a primary amine, and, as will be shown later, their structure must be of the type $\phi\cdot N{=}N\cdot N(CH_3)\cdot N{=}N\cdot\phi$. They are decomposed by alcoholic hydrochloric or sulphuric acid below 0°, and instead of giving two molecules of diazo-compound and one of amine, they give only one of diazo (together with one of alkylamine) and evolve one molecule of nitrogen. This formation of nitrogen must be due to a preliminary decomposition into a diazo-body and the triazene, which then breaks up in the normal manner; and the triazene so formed must, at least in the first instance, have its hydrogen atom attached to the nitrogen which carried the diazo-group:—

$$(\phi\cdot N{=}N{-})_2N\cdot CH_3 \longrightarrow \phi\cdot N_2Cl + \phi\cdot N{=}N\cdot NH\cdot CH_3 \longrightarrow \phi\cdot OH + N_2 + H_2N\cdot CH_3.$$

We must, therefore, admit that the decomposition with acids does take this abnormal course, and that the reaction with phenyl isocyanate, supported as it is by those with acid chloride and with diazo-salts themselves, gives a true indication of the formulae of these bodies.

To explain why it is that the same compound is obtained by diazotizing either of two aromatic amines and coupling it with the other, Goldschmidt has advanced a rather elaborate theory, involving the formation of addition-products with the acid present. This has been disproved by Dimroth, who showed that the same body was obtained from the azide of one aryl radical and the organo-magnesium compound of another, in whichever way the reaction was carried out. The theory is, indeed, obviously superfluous, the tautomerism being strictly analogous to that of the anti-diazo-hydrates and the nitrosamines:—

$$\begin{array}{l}Ar\cdot N\\ \quad\|\\ \quad N\cdot OH\end{array} \rightleftharpoons \begin{array}{l}Ar\cdot N\cdot H\\ \quad\quad|\\ \quad\quad N{:}O\end{array} \quad : \quad \begin{array}{l}Ar\cdot N\\ \quad\|\\ \quad N\cdot NH\cdot Ar_1\end{array} \rightleftharpoons \begin{array}{l}Ar\cdot N\cdot H\\ \quad\quad|\\ \quad\quad N{=}N\cdot Ar_1\end{array}.$$

The only important difference is that whereas in the first case the two tautomers belong to quite different chemical types, and so can sometimes be separated, in the case of the diazoamino-compounds they are so similar that no such separation is possible; this being what v. Pechmann has distinguished as 'virtual tautomerism'. The readiness with which the tautomeric change occurs is a further argument for the anti-formula. As we see in the case of the diazo-hydrates, such a change is characteristic of the anti- and not of the syn-compounds; and this is natural, since the change in position is less in the anti-series.

Incidentally this mobility of the imide hydrogen furnishes a conclusive proof of the correctness of the general structural formula (apart from stereo-chemical considerations) adopted for the diazoamino-compounds. Their method of formation only admits of three possible structures. First, they might be symmetrical ring compounds of the type

$$\begin{array}{c}NH\\ \diagup\quad\diagdown\\ Ar\cdot N\text{——}N\cdot Ar\end{array}.$$

This is at once ruled out by the fact that it is impossible to give an analogous formula to the condensation-product of diazobenzene hydrate with secondary amines like ethyl-aniline; and yet these bodies behave exactly like the ordinary diazoamino-bodies. Also it is impossible to explain the phenyl isocyanate reaction on this formula. Secondly, we might suppose them to be diazonium compounds, $\overset{\text{Ar·N·NH·Ar}}{\underset{\text{N}}{\|\|}}$; and thirdly, there is the usual diazoamino-formula Ar·N=N·NH·Ar. Now the identity of the two desmotropic unsymmetrical bodies which have just been discussed is conclusive in favour of the third formula. It is evident that the two pass into one another with great ease. On the third or diazo-formula this only requires the migration of the imide hydrogen, which, as we know from many parallel instances (such as that of the anti-diazohydrates), can occur very easily. But on the second or diazonium structure, it would require not only that the imide hydrogen should go from one nitrogen to the other, but also that the triply linked nitrogen should make a similar migration in the opposite direction:—

$$\overset{\text{Ar·N·NH·Ar}_1}{\underset{\text{N}}{\|\|}} \rightarrow \overset{\text{Ar·NH·N·Ar}_1}{\underset{\text{N}}{\|\|}};$$

and it is practically impossible that so great a change of structure should occur so easily.

The first diazoamino-compounds of the aliphatic series to be prepared belong to a quite different class from those mentioned above, and were discovered by Thiele. The starting-point of the investigation is the so-called diazoguanidine, which was discovered by Thiele[1] in 1892, and was re-examined in 1901 by Hantzsch and Vagt,[2] who showed that it is not a diazo-compound at all, but an azide. Thiele found that when amino-guanidine is treated with potassium nitrite in acid solution, a compound of the composition $CN_5H_3 \cdot HX$ is produced, which he supposed to be diazoguanidine:—

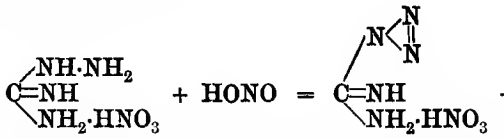
$$\begin{matrix} \text{NH·NH}_2 \\ \text{C=NH} \\ \text{NH}_2 \end{matrix}, \text{HNO}_3 + \text{ONOH} = \begin{matrix} \text{NH·N}_2\text{·ONO}_2 \\ \text{C=NH} \\ \text{NH}_2 \end{matrix} + 2\,\text{H}_2\text{O}.$$

This body, if it existed, would be a most remarkable substance. It would be a unique case of the diazotizing of an amino-group attached to nitrogen. Its properties are also very unusual for a diazonium compound. It is not decomposed even by warming the solution; it does not give off nitrogen when boiled; and on treatment with alkali it forms metallic azides. Its salts have an acid reaction, whereas a diazonium salt, with so positive a group as the guanidine residue, should be neutral. Moreover, on treatment with alkali a diazonium salt would first form the basic diazonium hydrate and then the alkaline diazotate. But this body first gives an indifferent unstable compound, and then breaks up into hydrazoic acid and cyanamide.

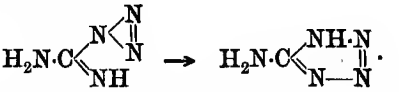
For all these reasons it is clear that the body is not a diazonium salt at all. On the contrary, all its reactions indicate that it is, as one would expect from its formation, an azide. The fact that it forms a salt is merely due to the presence

[1] *Ann.* **270**. 1. [2] *Ann.* **314**. 339.

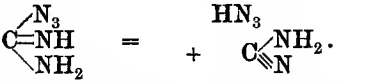
of the unmodified NH_2 group in the guanidine, and the equation which represents its formation is:—



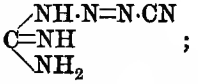
It is the nitrate of carbamide-imide-azide. The first effect of treating it with alkali is to liberate the free azide, which, if left to itself, rapidly changes into a ring compound, aminotetrazole:—



If the free azide is treated with more alkali it breaks up into hydrazoic acid and cyanamide:—

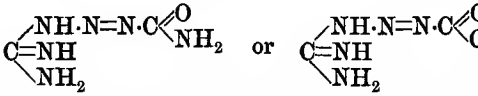


One remarkable reaction, which appears to favour Thiele's original view, is that when treated with potassium cyanide it is converted, like a diazonium salt, into a true diazocyanide:—



but Hantzsch has shown that other similar compounds, and especially the azide of urea,  , behave in the same way.

It is through these diazo-cyanides that Thiele[1] was able to prepare the diazoamino-compounds. In fact diazoguanidine cyanide is itself a diazoamino-compound, as is obvious from the formula. It is the amidine-nitrile of triazene dicarboxylic acid, $CO_2H{\cdot}NH{\cdot}N{=}N{\cdot}CO_2H$. Like all the diazo-cyanides it has the full nitrile character, and thus the CN group can be converted into an amide or an ester:—

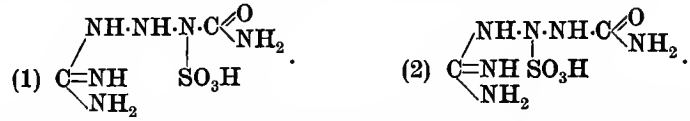


These bodies resemble the other diazoamino-compounds in giving off two-thirds of the triazene nitrogen as such on heating with dilute acids; but they differ from them in being decomposed by alkalies, to which the others are stable, and in being unaffected by cold concentrated acids.

Thiele has also succeeded in reducing these compounds to triazane derivatives or hydrazoamino-compounds. Like so many bodies with doubly linked nitrogen, they add on sulphurous acid to form the sulphonic acid of the reduced derivative. Since the product no longer behaves as a diazoamino-compound the reduction

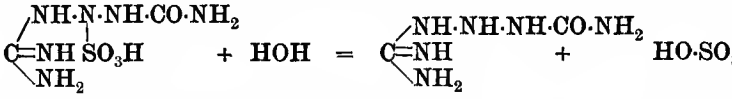
[1] *Ann.* **305**. 64 (1899).

must take place in the triazene group, and the only question is whether the SO_3H goes to the middle or the end of the nitrogen chain :—



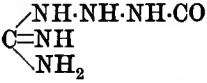
If the resulting substance had the first formula, it ought to be easily oxidized back to a diazoamino-derivative; but it is stable to oxidizing agents, and therefore must have the second formula.

All attempts to remove the SO_3H and replace it by hydrogen have failed. We should expect the reaction to take place as it does with phenyl-hydrazine :—



If it is warmed with acids sulphuric acid is split off, but the triazane which must be produced breaks up at once in a complicated manner, giving nitrogen, carbon monoxide, guanidine, and other products.

Thiele has also attempted to reduce these diazoamino-compounds directly. Under ordinary circumstances this gives, as it does in the aromatic series, a mixture of an amine and a hydrazine derivative. But if the body is carefully reduced with zinc dust and ammonium chloride, a colourless solution is obtained, which gives no reactions of the triazene. The product must have the N_3 chain intact, since on oxidation the diazoamino-compound is re-formed. It has strong reducing properties, and on warming readily decomposes into the same substances as are obtained by splitting off sulphuric acid from the sulphonic acid. It is evident, therefore, that in both cases the true triazane derivative,

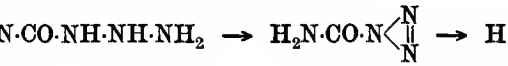


is formed, but that it is too unstable to be isolated. This great instability makes it improbable that any attempts to prepare triazane itself, $NH_2{\cdot}NH{\cdot}NH_2$, will succeed.

Darapsky[1] has endeavoured to form triazane derivatives by an extension of Schestakow's application of the Hofmann reaction. Schestakow obtained hydrazine compounds in this way from derivatives of urea (p. 187), and Darapsky applied the reaction to hydrazine derivatives of urea, which should produce triazanes, phenyl-semicarbazide, for example, giving phenyl-triazane thus :—

$$\phi{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NH_2 \longrightarrow \phi{\cdot}NH{\cdot}NH{\cdot}N{=}C{=}O \longrightarrow \phi{\cdot}NH{\cdot}NH{\cdot}NH_2.$$

But in no case was such a triazane obtained. The oxidation always proceeded further, with the formation either of an azide,



or of nitrogen itself. This affords a further illustration of the instability of the triazane derivatives.

[1] *J. pr. Ch.* [2] **76**. 433 (*C.* **08**. i. 452).

BUZANE OR TETRAZANE DERIVATIVES

Derivatives of buzane, $NH_2{\cdot}NH.NH{\cdot}NH_2$, are v. Pechmann's hydrotetrazones, which are formed by oxidizing hydrazones with amyl nitrite:—

$$\begin{matrix}\phi{\cdot}CH{=}N \\ | \\ \phi{\cdot}NH\end{matrix} + \begin{matrix}N{=}CH{\cdot}\phi \\ | \\ HN{\cdot}\phi\end{matrix} - H_2 = \begin{matrix}\phi{\cdot}CH{=}N & N{=}CH{\cdot}\phi \\ & | \\ \phi{\cdot}N{-}N & \cdot\phi\end{matrix}.$$

They all dissolve in concentrated sulphuric acid to give brilliantly coloured solutions; the compound whose formula has just been given (yellow needles, M.Pt. 180°) forming a deep blue solution. This is probably the origin of the Bülow reaction, the brilliant colour which hydrazones give with ferric chloride or potassium bichromate in concentrated sulphuric acid.

The hydrotetrazones are readily reduced back to hydrazones. When heated with alcoholic potash they undergo a remarkable change—a sort of reversal of the Beckmann reaction—to form benzil osazone:—

$$\begin{matrix}\phi{\cdot}C & HC{\cdot}\phi \\ \| & \| \\ N & N \\ | & | \\ \phi{\cdot}N{-}{-} & {-}N{\cdot}\phi\end{matrix} \rightarrow \begin{matrix}\phi{\cdot}C{-}{-} & {-}C{\cdot}\phi \\ \| & \| \\ N & N \\ | & | \\ \phi{\cdot}NH & HN{\cdot}\phi\end{matrix}.$$

The buzylene compounds or tetrazenes, as they are properly called (though they are generally known as tetrazones), are of two kinds, the derivatives of symmetrical tetrazene, $NH_2{\cdot}N{=}N{\cdot}NH_2$, and of unsymmetrical, $NH{=}N{\cdot}NH{\cdot}NH_2$. The former are obtained by oxidizing the unsymmetrical secondary hydrazines with mercuric oxide[1]:—

$$(CH_3)_2N{-}NH_2 + O_2 + H_2N{-}N(CH_3)_2 = (CH_3)_2N{\cdot}N{=}N{\cdot}N(CH_3)_2 + 2\,H_2O.$$

They are strongly basic colourless oily substances, easily volatile with steam, which explode when heated to a somewhat high temperature. They reduce silver nitrate in the cold, and form very soluble and unstable salts. When the solution is boiled, half the nitrogen comes off as such, with the formation of an amine and an aldehyde.

The aromatic tetrazones are very similar.[2]

The derivatives of unsymmetrical tetrazene, $NH{=}N{\cdot}NH{\cdot}NH_2$, are obtained by the action of diazo-compounds on hydrazines in acetic acid solution,[3] and hence are known as diazo-hydrazides. Their structure has been determined in the following way.[4] Benzal-benzyl-hydrazone, $\phi{\cdot}CH_2{\cdot}NH{\cdot}N{=}CH{\cdot}\phi$, combines with nitrophenyl-diazo-hydrate to form a diazo-hydrazide which can only have the formula:—

$$NO_2{\cdot}C_6H_4{\cdot}N{=}N{-}N\begin{matrix}N{=}CH{\cdot}\phi \\ CH_2{\cdot}\phi\end{matrix}.$$

This same compound is formed from the diazo-hydrazide got by treating with

[1] Cf. Franchimont, van Erp, *Rec. Trav.* **14.** 317 (1896).
[2] Cf. Wieland, *Ber.* **41.** 3498 (1908).
[3] Wohl, *Ber.* **26.** 1587 (1893).
[4] Wohl, Schiff, *Ber.* **33.** 2741 (1900).

benzaldehyde the diazo-hydrazide obtained from nitrophenyl-diazo-hydrate and benzyl-hydrazine. Hence this last-named body must have the structure

$$NO_2 \cdot C_6H_4 \cdot N{=}N \cdot N\langle \begin{matrix} NH_2 \\ CH_2 \cdot \phi \end{matrix},$$

and in general the diazo-hydrazides must be of the type $Ar \cdot N{=}N \cdot N\langle \begin{matrix} NH_2 \\ Ar \end{matrix}$.

They are unstable basic substances, which break up on reduction into phenyl-hydrazine and two molecules of hydrazine.

BIS-DIAZOAMINO-COMPOUNDS

These bodies, containing a chain of five nitrogen atoms, are formed by the condensation of two molecules of a diazo-compound with one molecule of ammonia or a primary amine[1]:—

$$\phi \cdot N{=}N \cdot OH + NH_3 + HO \cdot N{=}N \cdot \phi = \phi \cdot N{=}N \cdot NH \cdot N{=}N \cdot \phi + 2\,H_2O.$$

It is conceivable that the reaction might go in a different way, diazobenzene combining, for example, with methylamine to give a body $\begin{matrix} \phi \cdot N \cdot N{=}N \cdot CH_3 \\ | \\ \phi \cdot N{=}N \end{matrix}$.

Now these bodies are also formed by the action of a diazo-compound on an aryl-alkyl-triazene, and if they had the unsymmetrical formula one would obtain a different product by treating phenyl-methyl-triazene with diazotoluene and tolyl-methyl-triazene with diazobenzene. Experiment[2] showed, however, that the two products were identical, so that the bis-diazoamino-compound must have the symmetrical structure $Ar \cdot N{=}N \cdot N(Alk)N{=}N \cdot Ar$. These bodies are coloured, generally very explosive substances. When boiled with alkali they break up in the normal manner into two molecules of phenol, one of amine, and two of nitrogen. Their singular decomposition with acids has already been mentioned. Those which are derived from alkylamines give, even at 0°, one molecule of diazo, one of nitrogen, one of phenol, and one of alkylamine. This is no doubt due to the preliminary formation of the diazoamino-compound:—

$$(Ar \cdot N{=}N{-})_2N \cdot CH_3 \longrightarrow Ar \cdot N{=}N \cdot OH + Ar \cdot N{=}N \cdot NH \cdot CH_3$$
$$\longrightarrow Ar \cdot OH + N_2 + H_2N \cdot CH_3.$$

Bis-diazoamino-benzene itself, instead of giving, as we should expect, phenol, nitrogen, and ammonia, forms phenol, aniline, and nitrogen. This may be explained in a similar way, by the intermediate production of phenyl-triazene:—

$$(\phi \cdot N{=}N{-})_2NH \longrightarrow \phi \cdot N{=}N \cdot OH + \phi \cdot N{=}N \cdot NH_2 \longrightarrow \phi \cdot OH + N_2 + \phi \cdot NH_2 + N_2.$$

OCTAZONES

The longest known chain of nitrogen atoms consists of 8, and occurs in the octazones. These curious bodies were obtained by Wohl and Schiff[3] by oxidizing the diazo-hydrazides with potassium permanganate:—

$$2\,\phi \cdot N{=}N \cdot N\phi \cdot NH_2 + 2\,O = \phi \cdot N{=}N \cdot N\phi \cdot N{=}N \cdot N\phi \cdot N{=}N \cdot \phi + 2\,H_2O,$$

the reaction being exactly analogous to that by which a hydrazine is converted into a tetrazone.

The octazones are yellow bodies which are, as one might expect, very unstable and highly explosive.

[1] v. Pechmann, Frobenius, *Ber.* **27**. 703, 898 (1894); **28**. 170 (1895).
[2] Dimroth, Eble, Gruhl, *Ber.* **40**. 2390 (1907). [3] *Ber.* **33**. 2741 (1900).

CHAPTER XV

URIC ACID DERIVATIVES

THESE bodies are, strictly speaking, heterocyclic compounds, but from their close relationship to the open-chain compounds, and the ease with which they pass into them, they occupy a somewhat anomalous position, and are most conveniently treated as a class by themselves, before we come to deal with the various types of nitrogenous rings.

The central point of the whole group is uric acid itself; but this cannot be discussed until after the consideration of some of the simpler compounds from which it is built up.

Urea, as a substituted ammonia, can combine with acids with loss of water to form a series of compounds analogous to the amides. These are known as *ureides*: e. g.:—

$$CO(NH_2)_2 + HO\cdot CO\cdot CH_3 = CO(NH\cdot CO\cdot CH_3)(NH_2) + H_2O:$$

Acetyl urea.

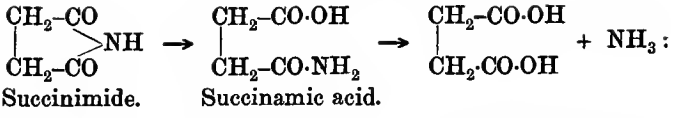
as $$NH_3 + HO\cdot CO\cdot CH_3 = NH_2\cdot CO\cdot CH_3 + H_2O.$$

If this condensation occurs twice we get di-ureides, such as $CO(NH\cdot CO\cdot CH_3)_2$.

But if, instead of two molecules of a monobasic acid, one molecule of a dibasic acid combines with one of urea, the resulting compound contains a closed ring. Such compounds are called cyclic ureides: an example is oxalyl-urea or parabanic acid, $CO(NH{-}CO)_2$.

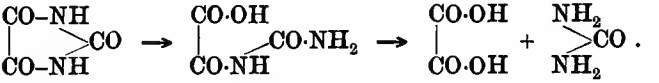
It is unfortunate that as many members of this group were known long before their formulae were made out, they have received a series of irrational names; but these names are now so well established and so constantly employed that they cannot be altogether neglected.

In behaviour the cyclic ureides show a certain resemblance to the imides of the dibasic acids, such as succinimide. There is the same tendency to break the ring in the presence of alkali, with the formation of mono-ureides which are at the same time acids: the ultimate effect of alkali being of course to split up the compound completely into the dibasic acid and urea, or ammonia and carbonic acid. Compare



Succinimide. Succinamic acid.

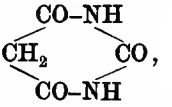
and



Oxalyl-urea. Oxaluric acid.
Parabanic acid.

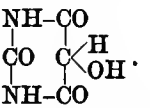
Oxalyl-urea is obtained from oxalic acid and urea by the action of phosphorus pentachloride. Bromine converts it into oxaluric acid, which is changed back into oxalyl-urea by phosphorus oxychloride, and is broken up by alkali into urea and oxalic acid.

Of greater importance is malonyl-urea or barbituric acid,

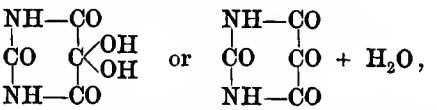


which may be got from malonic acid, urea, and phosphorus oxychloride. It is a crystalline substance which is broken up into its constituents on boiling with alkali. The hydrogen atoms of the methylene group, as in malonic acid itself, are very reactive. They can be replaced by bromine, $-NO_2$, =NOH, &c., with great ease, and thus indirectly by other groups as well. Malonyl-urea acts as an acid, forming salts in which these hydrogens are replaced by metal; and these salts, when treated with alkyl iodide, give C-alkyl derivatives. In these ways a series of derivatives of malonyl-urea have been prepared which have been of the greatest value in determining the constitution of the members of the uric acid group.

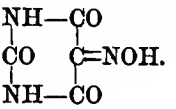
For example, if dibromo-barbituric acid is reduced with hydrogen sulphide, it gives hydroxy-barbituric acid, dialuric acid, or tartronyl-urea,



Again, the dihydroxy-derivative, mesoxalyl-urea,



is alloxan. This is one of the oxidation-products of uric acid, and its constitution is shown by the fact that its oxime is identical with the isonitroso-compound obtained from barbituric acid and nitrous acid, which must be

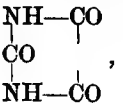


This last body is known as violuric acid.[1] It is broken up by alkali into urea and isonitroso-malonic acid.

Fuming nitric acid converts barbituric acid into the nitro-derivative, dilituric acid (whose formula is given below), which is also formed by the oxidation of violuric acid.

Finally, by the reduction of violuric or of dilituric acid is formed amino-barbituric acid or uramil.

The formulae and common names of the more important of these compounds are given in the following table. They are all derived from barbituric acid or malonyl-urea by modifying the methylene group. The ring represents the group



which they all contain.

 Malonyl-urea, barbituric acid.

 Hydroxy-malonyl-urea, dialuric acid.

 or  Dihydroxy-malonyl-urea, mesoxalyl-urea, alloxan.

 Isonitroso-malonyl-urea, violuric acid.

 Nitro-malonyl-urea, dilituric acid.

 Amino-barbituric acid, uramil.

Uric Acid

Uric acid was discovered in urinary calculi by Scheele in 1776, and simultaneously by Bergmann. It occurs in various parts of the animal organism—muscles, blood, urine, &c.—especially in the carnivora; also in guano, up to 25 per cent., and to a still greater extent—90 per cent.—in the excrement of serpents. It forms small crystals, without smell or taste. It is insoluble in alcohol and ether, but dissolves in 10,000 parts of water at 18·5°, and in 1,800 at 100°.

[1] Violuric acid is remarkable for the changes of colour which it undergoes. In the solid state it is colourless : in solution, especially in the presence of small quantities of bases, it is blue (see Donnan, Schneider, *J. C. S.*, **1909**. 956). Its esters are colourless, and its salts in the solid state are colourless, yellow, red, and blue. The colourless salts and the esters are evidently of the type  . The coloured salts must have three other structures, but it is at present quite uncertain what these may be. Cf. Hantzsch, *Ber.* **42**. 966 ; Hantzsch, Isherwood, ib. 986 ; Hantzsch, Issaias, ib. 1000 (1909).

It is a feeble dibasic acid. Its alkaline salts are mostly very insoluble, and are highly hydrolysed in solution. The potassium salt requires 800 parts of water to dissolve it, and the sodium and ammonium salts a still larger quantity. The lithium salt is more soluble, dissolving in 368 parts of cold water, and the salt of piperazine, $NH\begin{<}CH_2-CH_2\\CH_2-CH_2\end{>}NH$, still more so, requiring only fifty parts at 17°. Hence lithium, and more recently piperazine, have been used in medicine to remove deposits of uric acid in the body in gout and rheumatism; though it is doubtful whether their use, or at any rate this explanation of it, does not rest on a physico-chemical error.

The first systematic investigation[1] of uric acid was that of Liebig and Wöhler (1826–1838), who discovered an immense number of its reactions, and converted it into a series of other substances, many of which were already known to exist in nature. But their work threw little or no light on its constitution. Our knowledge of this is due in the first place to Baeyer, who began his researches on it in 1863.[2] He showed that the whole class of substances included in the group could be regarded as derivatives of barbituric acid, which he proved to be malonyl-urea from its hydrolysis to ammonia, carbon dioxide, and malonic acid. He also prepared from it the hydroxy- (dialuric acid), the keto- (alloxan), the isonitroso- (violuric acid), and the nitro-derivative (dilituric acid). He proved the constitution of the last two by reducing them to uramil, which was shown to be amino-malonyl-urea by its giving the hydroxy-compound (dialuric acid) when treated with nitrous acid. This uramil combines with cyanic acid to give a body which Baeyer called pseudo-uric acid. The reaction must go in this way:—

$$\begin{array}{l}NH-CO\\|\quad\ |\\CO\quad CH\cdot NH_2\\|\quad\ |\\NH-CO\end{array} + C\begin{<}\begin{array}{l}NH\\O\end{array} = \begin{array}{l}NH-CO\\|\quad\ |\\CO\quad CH\cdot NH\cdot CO\cdot NH_2\\|\quad\ |\\NH-CO\end{array}.$$

Pseudo-uric acid differs in composition from uric acid only by containing the elements of one molecule of water more; and Baeyer hoped to be able to convert it into uric acid by the action of dehydrating agents. But he could not bring about this change, though E. Fischer subsequently showed that it is possible.

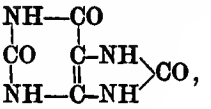
In 1875 Medicus[3] published a most remarkable paper on the constitution of this group of compounds. He produced hardly any new facts; but sometimes on the basis of facts already known, and sometimes, apparently, on no basis at all, he suggested formulae for nearly every known compound of the group—uric acid, xanthine, caffeine, theobromine, guanine, and hypoxanthine. The singular point is that with the exception of the position of one of the methyl groups in theobromine, all the formulae which Medicus proposed are absolutely correct; although it was not until the most recent work of Fischer, in which he revised and modified many of his own previous formulae, that they were recognized as being so.

We are at present concerned only with uric acid. For this Medicus proposed the now accepted formula:—

[1] For a summary of the history of this subject see Lachman, *Spirit of Organic Chemistry*.

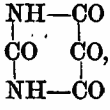
[2] *Ann.* **127**. 1, 199.

[3] *Ann.* **175**. 236.



on the following grounds:—

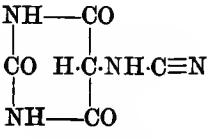
1. On heating with acids it gives glycocoll, ammonia, and carbon dioxide (Strecker).

2. On oxidation it gives alloxan,  and urea (Liebig and Wöhler).

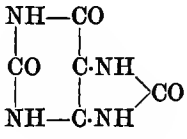
3. On treatment with alkaline permanganate it gives allantoin, which breaks up into glyoxylic acid, CHO·COOH, and urea.

It is obvious that these arguments are quite insufficient to establish his formula, and it is not easy to see how they led him to adopt it.

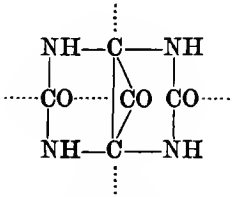
In 1882 E. Fischer[1] published a detailed examination of uric acid and its derivatives, in which the constitution of uric acid was finally determined, in accordance with Medicus's suggestion, but on much more satisfactory evidence. Baeyer had shown that uric acid must be formed from malonyl-urea by the addition of another molecule of urea and the loss of four atoms of hydrogen and two of oxygen. The whole question was how this loss occurred. Baeyer had proposed a formula in which no second ring was formed; Medicus had suggested the one which has just been given; while Fittig had put forward yet a third formula, also assuming the production of a second ring, and attractive on account of its symmetry:—



Baeyer.



Medicus.



Fittig.

Before the publication of E. Fischer's paper, Fittig's view was the one generally adopted. It is to be noticed that his formula is symmetrical about both of the dotted lines, so that all the four NH groups are similarly related to the rest of the molecule.

Fischer showed in the first place that there are four imide (NH) groups in uric acid; for a tetramethyl derivative can be prepared which on saponification yields all its nitrogen in the form of methylamine, and gives no ammonia. Hence all the four methyls are attached to the four nitrogen atoms. This makes Baeyer's formula impossible, as it only contains three NH groups, the other hydrogen being attached to carbon; but it does not decide between Medicus and Fittig.

Secondly, Fischer obtained two different monomethyl-uric acids. Hence the compound is not symmetrical, and Fittig's formula must be rejected. More-

[1] *Ann.* **215.** 253.

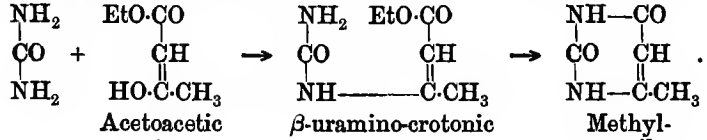
over, one of these monomethyl derivatives on oxidation gives alloxan and methyl-urea, while the other gives methyl-alloxan and urea; showing that one of the NH groups is not contained in the alloxan or barbituric acid ring. The isomerism and behaviour of the numerous other methyl derivatives prepared by Fischer are found to be in full accordance with Medicus's formula; but the two reactions which have been mentioned are the most important, and are in themselves quite a sufficient proof.

The three most important syntheses of uric acid are:—

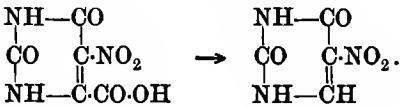
1. From acetoacetic ester (Behrend, 1888).
2. From malonic acid, begun by Baeyer in 1863, and completed thirty-two years later (1895) by E. Fischer.
3. From cyanacetic acid (W. Traube, 1900).

1. *Behrend's Synthesis*

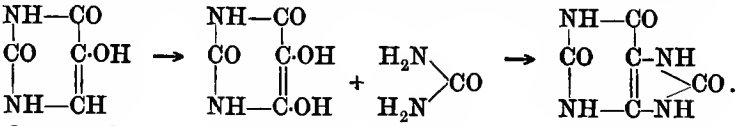
Acetoacetic ester condenses in the enolic form with urea to give β-uramino-crotonic ester; this on saponification gives the corresponding acid, which loses water to form a cyclic ureide, methyl-uracil:—



Nitric acid nitrates methyl-uracil in the CH group, while the methyl is oxidized to carboxyl, the product being nitro-uracil carboxylic acid. When this is boiled with water it loses carbon dioxide and forms nitro-uracil:—



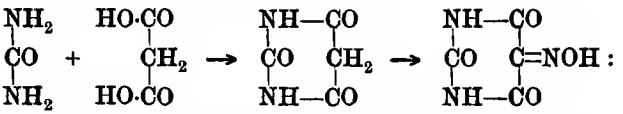
Nitro-uracil, on treatment with tin and hydrochloric acid, is converted partly into amino-uracil and partly also into oxy-uracil: the former dissolves in the acid liquid, while the latter remains undissolved, and so can be filtered off. The oxy-uracil is oxidized by bromine water to dioxy-uracil (isodialuric acid), which condenses with urea in the presence of sulphuric acid to give uric acid:—



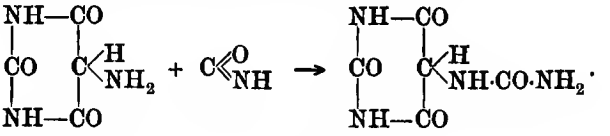
2. *Baeyer and Fischer's Synthesis*

The first part of this synthesis has already been described. Baeyer showed that malonic acid condenses with urea in the presence of phosphorus oxychloride

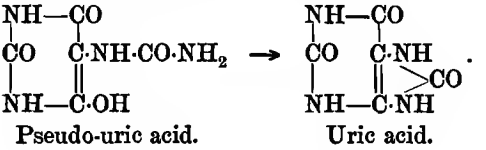
to give malonyl-urea or barbituric acid: that this is converted by nitrous acid into the isonitroso-compound, violuric acid:—



and that this on reduction gives amino-malonyl-urea or uramil, which condenses with cyanic acid to form pseudo-uric acid:—



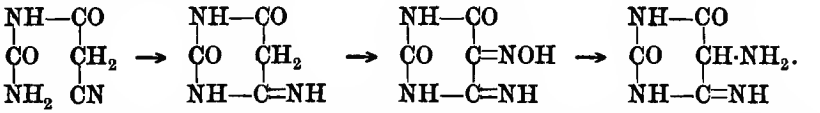
Beyond this point Baeyer was unable to go. All that was wanted was that the pseudo-uric acid should lose one molecule of water to form uric acid; but he could not make it do this. It was not until thirty-two years later that E. Fischer showed that the reaction can be brought about by treatment with fused oxalic acid, and even by boiling with mineral acids, uric acid being produced. This change is most simply expressed if we suppose the pseudo-uric acid to react in the enolic form:—



Pseudo-uric acid. Uric acid.

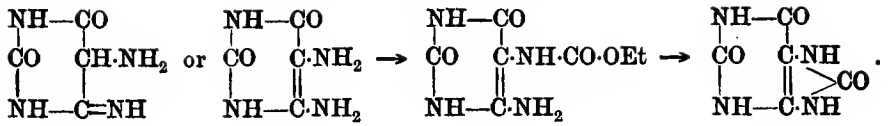
3. *Traube's Synthesis*

This work,[1] which is subsequent to Fischer's investigations, starts with cyanacetic acid. Traube finds that cyanacetic acid readily condenses with urea in presence of phosphorus oxychloride to give cyanacetyl-urea. This body when treated with dilute alkalies is converted into the isomeric cyclic pyrimidine derivative, which is imino-barbituric acid. This yields with nitrous acid an isonitroso-derivative, which on reduction gives the corresponding amino-compound:—

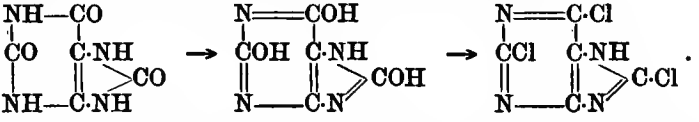


This last body, which may also be written in a tautomeric form as a diamino-compound, when shaken with chlorocarbonic ester in alkaline solution, gives a urethane; and the sodium salt of this urethane, when heated to 180–190°, loses water and forms the sodium salt of uric acid:—

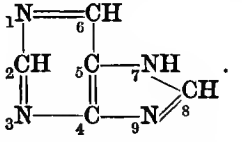
[1] *Ber.* **33**. 1371, 3035 (1900).



The other derivatives must be dealt with more briefly, beginning with the mother substance of the whole group, which historically was the last to be prepared. Uric acid contains three carbonyls adjacent to imide groups. Each of these carbonyls is capable of passing over, in the presence of a suitable reagent, into an enol (hydroxyl) group. Thus on treatment with phosphorus oxychloride these three hydroxyls are replaced by chlorine :—

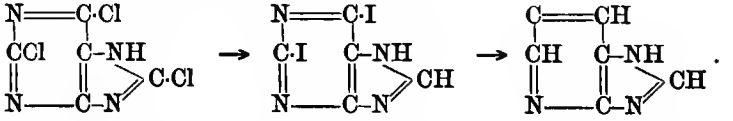


Now all the complicated uric acid derivatives, such as caffeine and xanthine, contain this carbon and nitrogen skeleton; and as it is necessary to have a rational nomenclature for them, Fischer proposed in 1884 to call the then hypothetical hydrogen compound, of which the last-mentioned body is the trichloro-substitution product, purine (from purum and uricum), and to name the other substances from it, the atoms being numbered thus :—



The preparation of purine itself presented extraordinary difficulties, as all the usual reducing agents when applied to trichloro-purine either failed to reduce it or broke up the molecule altogether. It was not until 1898 that Fischer succeeded in obtaining it, which he did as follows.[1]

Trichloro-purine, from uric acid and phosphorus oxychloride, was treated with hydriodic acid and phosphonium iodide at 0°. This replaces one chlorine by hydrogen and the other two by iodine. The resulting diiodo-purine can be shown to have the iodine in the positions 2 and 6. When it is reduced with zinc dust alone in boiling aqueous solution, the two iodine atoms are replaced by hydrogen, and purine is produced :—



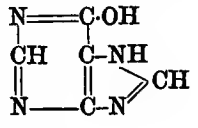
Trichloro- Diiodo- Purine.

Purine is a colourless crystalline substance melting at 216°. It volatilizes partly undecomposed. It is remarkably soluble in water and alcohol, but only slightly in ether and chloroform. It combines with one equivalent of

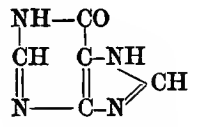
[1] *Ber.* **31**. 2550.

acids to form salts such as $C_5H_4N_4 \cdot HNO_3$. It also forms salts with bases, the alkaline salts being excessively soluble in water. It is fairly stable to oxidizing agents, not being attacked by chromic acid even on boiling, nor oxidized by potassium permanganate at once in the cold.

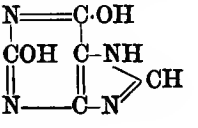
The numerous naturally occurring derivatives of purine, whose constitution has been established by E. Fischer, may be divided into three classes, according as they are derived from mono-, di-, or trihydroxy-purine. The last of these is of course uric acid itself, written on the trienolic formula: while the mono-hydroxy-compound is hypoxanthine, and the di-hydroxy- is xanthine, both of which substances occur in the animal organism :—



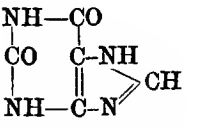
or



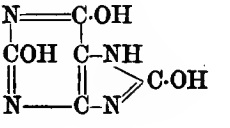
6-Oxy-purine.
Hypoxanthine.



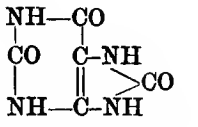
or



2,6-Dioxy-purine.
Xanthine.



or



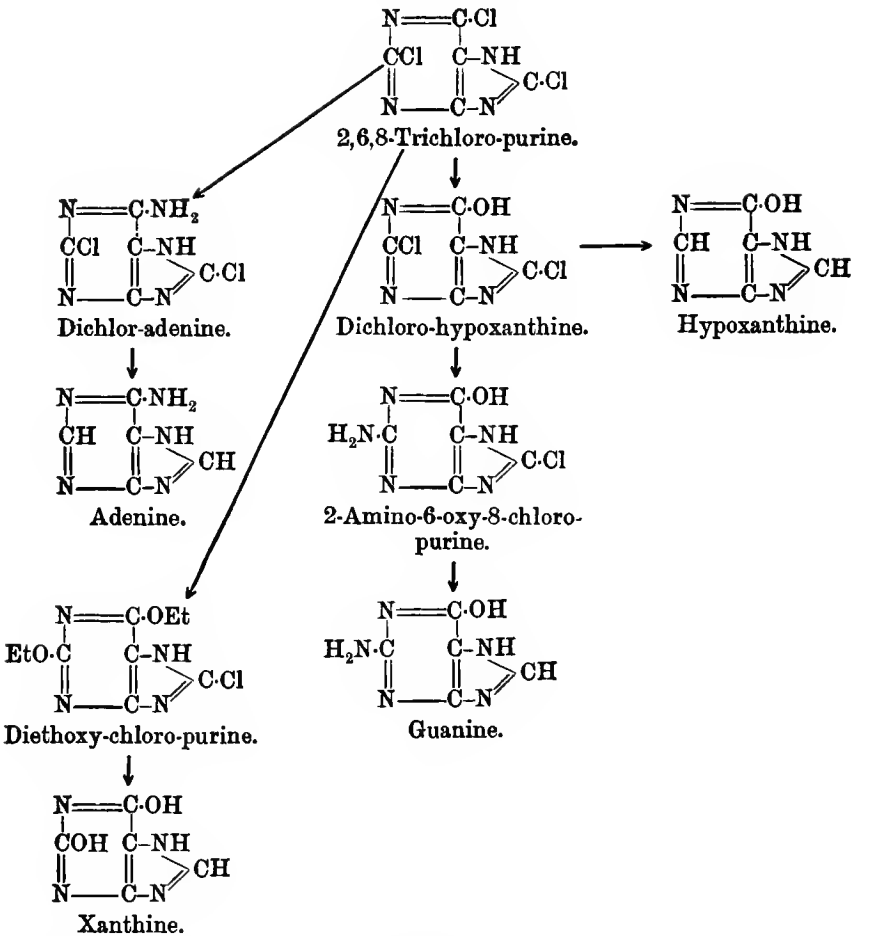
2,6,8-Trioxy-purine.
Uric acid.

The compounds of this group may be prepared from uric acid.[1] This is first converted into trichloro-purine. Of the three chlorine atoms which this body contains, the most mobile is in position 6 ; while that at 2 can also be readily though less easily removed. The other chlorine atom (at 8) is more firmly attached. It is on these differences that the whole of these syntheses depend.

If trichloro-purine is treated with aqueous ammonia, the chlorine at 6 is replaced by NH_2, giving dichlor-adenine. If it is treated with aqueous potash, the same chlorine atom is replaced by hydroxyl, giving dichloro-hypoxanthine. These two bodies can have the remaining chlorine atoms replaced by hydrogen, by treatment with hydriodic acid, being thereby converted respectively into adenine and hypoxanthine. Further, alcoholic ammonia acts on dichloro-hypoxanthine to replace the next chlorine atom (at 2) by NH_2, giving 2-amino-6-oxy-8-chloro-purine, which is reduced by hydriodic acid to guanine. The constitution of this body as a guanidine derivative is shown by its splitting off guanidine on oxidation.

Finally, if trichloro-purine is treated with sodium ethylate, the two chlorine atoms at 6 and 2 are replaced by ethoxy-groups, forming diethoxy-chloro-purine, and when this is reduced the chlorine is replaced by hydrogen at the same time that the ethoxy-groups are saponified, and 2,6-dioxy-purine or xanthine is formed. These relationships are shown in the following table :—

[1] E. Fischer, *Ber.* **30.** 2220, 2226 (1897). A brief but clear account of the relationships and syntheses of these bodies is given in Richter's *Organische Chemie*, vol. i, pp. 609–14 (10th ed., 1903).



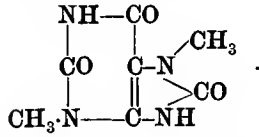
These four bodies all occur naturally in various animal substances, and adenine and xanthine also in tea. Their constitution is established by various reactions. Thus nitrous acid converts adenine into hypoxanthine, and guanine into xanthine: while xanthine itself is converted by the introduction of three methyl groups into caffeine, which belongs to the next class of uric acid derivatives.

This class consists of the methyl derivatives of xanthine: heteroxanthine (7-methyl-xanthine), theobromine (3,7-dimethyl-xanthine), paraxanthine (1,7-dimethyl-xanthine) theophylline (1,3-dimethyl-xanthine), and caffeine (1,3,7-trimethyl-xanthine).

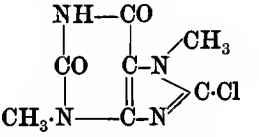
They all occur in nature. Caffeine, the most important of them, is found to the extent of 0·5–2 per cent. in coffee, and 2–4 per cent. in tea, whence it has also been called theine. The formulae of these bodies are established by their syntheses. 3,7-Dimethyl-uric acid is converted by phosphorus oxychloride into a mono-chloro-derivative, which is chloro-theobromine, and gives theobromine on reduction. Theobromine when treated with phosphorus oxy-

chloride and pentachloride, has one of its methyls removed, and the two hydroxyls replaced by chlorine. When the body so formed is treated with ammonia and the product oxidized with chlorine, it gives guanidine. This shows that the remaining methyl group cannot be at 3 (or it would give methyl-guanidine), and so must be at 7. When this body is treated with fuming hydrochloric acid the chlorine atoms are removed, with the production of 7-methyl-xanthine, which is heteroxanthine.

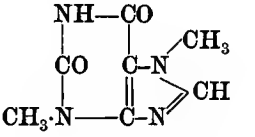
On the other hand, if this 7-methyl-2,6-dichloro-purine is treated with potash, only the chlorine at 6 (the most mobile) is saponified. The product on methylation takes up a methyl group at 1, and the body so formed is hydrolysed by hydrochloric acid to give paraxanthine.



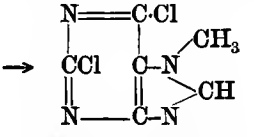
3,7-Dimethyl-uric acid.



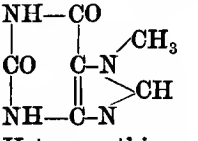
Chloro-theobromine.



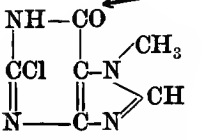
Theobromine.



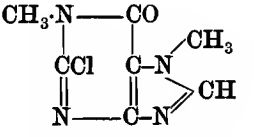
7-Methyl-2,6-dichloro-purine.



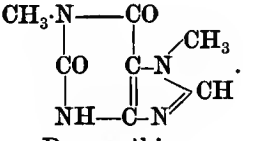
Heteroxanthine.



7-Methyl-6-oxy-2-chloro-purine.

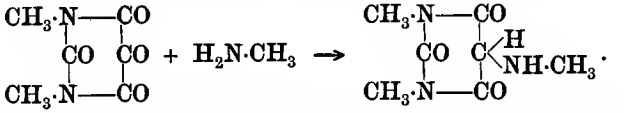


1,7-Dimethyl-6-oxy-2-chloro-purine.

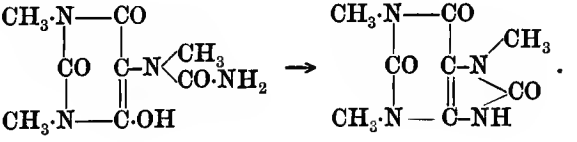


Paraxanthine.

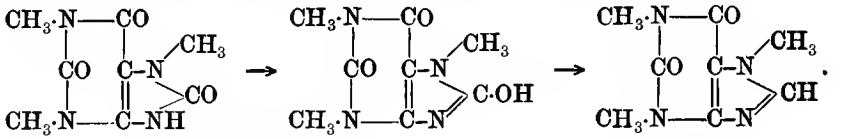
Caffeine can be obtained by the methylation of xanthine, and therefore is trimethyl-xanthine. Its formula is proved by its synthesis from dimethyl-alloxan, which can only have one constitution. This body combines with methylamine in presence of sulphur dioxide to give trimethyl-uramil :—



This, like uramil itself, condenses with cyanic acid, forming trimethyl-pseudo-uric acid : and this loses water, when treated with mineral acids, to give trimethyl-uric acid :—

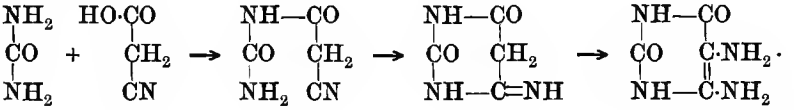


This is a substance already known as hydroxy-caffeine, and it yields caffeine on reduction. This reduction obviously consists in the replacement of the hydroxyl of the enol form by hydrogen, and so can only take place in one way :—

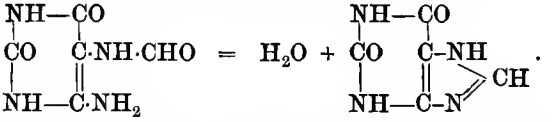


Hydroxy-caffeine. Caffeine.

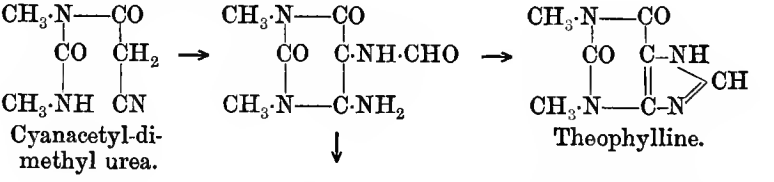
Any of the other syntheses of uric acid may be modified so as to produce the other members of the group. Traube, for example, as has already been mentioned, converted cyanacetyl urea into a pyrimidine, which, on treatment with nitrous acid and subsequent reduction, gave a diamino-derivative.



The product condenses with formic acid to give a formyl derivative, whose sodium salt loses water to form the sodium salt of xanthine :—

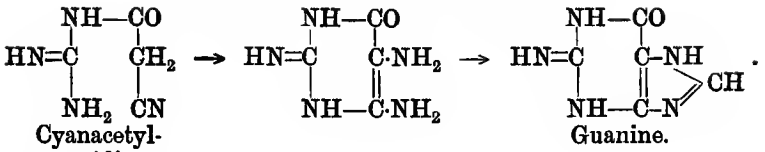


If we start with symmetrical dimethyl urea instead of urea, and take it through the same series of reactions, we arrive at a dimethyl-formyl compound, which can then be further treated in two ways. If it is heated, it readily loses water to give 1,3-dimethyl-xanthine, which is theophylline. On the other hand, if it is treated with sodium ethylate and methyl iodide, the acidic imide hydrogen next to the formyl group is replaced by methyl, and the product condenses to caffeine :—



Cyanacetyl-dimethyl urea. Theophylline. Caffeine.

So also guanidine gives cyanacetyl-guanidine, which can be transformed in an analogous way into guanine :—



Cyanacetyl-guanidine. Guanine.

Further details as to these syntheses, and further evidence as to the structure of the products, may be found in Fischer's original papers. But it is to be observed that while Fischer's proof[1] of the formula of uric acid itself has never been disputed, in his first and very important paper on caffeine,[2] though many of his proofs are of great value and still hold good, yet he adopts the view that all the xanthine derivatives, such as caffeine and guanine, contain a different nucleus from uric acid; and this false theory was not corrected until his last series of papers in *Ber.* **30, 31, 32** (1897–8–9), of which the most important is in *Ber.* **32.** 435, which contains a summary of the whole group, and a history of the steps by which the respective formulae were established.

[1] *Ber.* **17.** 1776 (1884).

[2] *Ann.* **215.** 253 (1882).

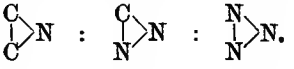
DIVISION IV

RING COMPOUNDS

Of the large number of known compounds containing nitrogen in a closed ring, only a few of the most important can be discussed.

The simplest method of classification is to divide them into groups according to the total number of atoms in the ring, subdividing each group according to the number of nitrogen atoms which the ring contains.

The first group thus consists of the 3-rings; and of this there are three subdivisions :—



CHAPTER XVI

3-RINGS AND 4-RINGS

I. 3-RINGS. C_2N

Of this subgroup very few representatives are known, and only one is of any importance. This is ethylene imine, $\begin{matrix}CH_2\\|\\CH_2\end{matrix}\!\!>\!NH$. When bromethylamine, $CH_2Br{\cdot}CH_2{\cdot}NH_2$, is treated with potash it loses hydrobromic acid, forming a base, C_2H_5N. This may have either of two formulae, $CH_2{=}CH{\cdot}NH_2$, vinylamine, or $\begin{matrix}CH_2\\|\\CH_2\end{matrix}\!\!>\!NH$, ethylene imine, according as the hydrogen of the hydrobromic acid comes from the CH_2 or the NH_2. The compound behaves in many respects like an unsaturated body. It readily adds on hydrochloric acid to form chlorethylamine, $CH_2Cl{\cdot}CH_2{\cdot}NH_2$, and sulphurous acid to give taurine, $\begin{matrix}CH_2{\cdot}NH_2\\|\\CH_2{\cdot}SO_3H\end{matrix}$. Hence it was at first supposed to be vinylamine.

The resemblance of its mode of formation, and to a certain extent of its properties, to those of trimethylene imine, $\begin{matrix}CH_2{-}NH\\|\quad\;|\\CH_2{-}CH_2\end{matrix}$, led Marckwald[1] to suspect that it might have the ring formula. The ordinary reagents for the NH_2 group, such as nitrous acid, cannot be applied to this substance on account of its instability. Marckwald therefore used the Hinsberg reaction with benzene sulphonic chloride, which has already been described (p. 19), and showed that the body gave a sulphonamide insoluble in alkali. It follows that it must be a secondary amine, i. e. ethylene imine.

This substance is a colourless liquid soluble in water, which attacks the skin and smells strongly of ammonia. Its unsaturated character is clearly due to the great strain in the ring. It is of interest as the first member of the group of polymethylene imines, including trimethylene imine, pyrrolidine (tetrahydropyrrol), and piperidine.

II. CN_2 GROUP. DERIVATIVES OF DIAZOMETHANE

The bodies contained in this group are the so-called fatty diazo-compounds. The name is too well established to be given up, but it is unfortunate and misleading, as it suggests a resemblance to the aromatic diazo-compounds, whereas the fatty diazo-compounds, though allied to them, are, as ring compounds, very different both in structure and in behaviour.

Tho first member of the group to be discovered was diazoacetic ester,

[1] Howard, Marckwald, *Ber.* **32**. 2036 (1899)

obtained by Curtius in 1883 by the action of nitrous acid on glycocoll ester hydrochloride. The mother substance, diazomethane, $CH_2{<}^{N}_{N}$, was not discovered by v. Pechmann till 1894.[1] It is formed by the action of alkalies on various nitroso-derivatives of methylamine, containing the group $CH_3{\cdot}N{\cdot}NO$, the one most commonly employed being nitrosomethyl-urethane. This reaction, as has already been explained, must proceed in several stages. The first is no doubt the formation of an unstable nitroso primary amine: this then changes into the isomeric open-chain diazo-compound, which can actually be isolated, and this again loses water to form the diazomethane:—

$$CO{<}^{OEt}_{N{<}^{NO}_{CH_3}} \rightarrow CH_3{\cdot}N{<}^{H}_{NO} \rightarrow CH_3{\cdot}N{=}N{\cdot}OH \rightarrow CH_2{<}^{N}_{N} + H_2O.$$

Pechmann's method[2] was to dissolve nitroso-methyl-urethane in ether and add a 25 per cent. solution of potash in methyl alcohol. The mixture is warmed on a water bath, when a yellow liquid distils over, which is a solution of the gaseous diazomethane in ether. The yield is about 50 per cent.

The true open-chain diazo-compound, which is an intermediate product in this reaction, may be described here, though it is strictly analogous to the aromatic diazo-compounds. It was obtained by Hantzsch[3] by treating the urethane with excessively concentrated aqueous potash, or with ethereal potassium ethylate. The urethane, without any ether, is dropped into the very concentrated potash at 0°. In a few moments the salt, $CH_3{\cdot}N{=}NOK,H_2O$, crystallizes out. It is extraordinarily sensitive to water, a few drops of which change it explosively into diazomethane and potash. This is because, as the salt of a very weak acid (even weaker than diazobenzene hydrate), it is very readily hydrolysed; and the excessively unstable hydrate instantly loses water to form diazomethane. The same fact explains why this body is not formed in v. Pechmann's method of preparation. The methyl alcohol, which must be present in considerable excess, owing to its comparatively slight power of dissolving potash, causes sufficient hydrolysis to bring about this change.

Diazomethane can also be made,[4] though only in very small quantity, by the reduction of methyl nitramine, $CH_3{\cdot}NH{\cdot}NO_2$; and in rather better yield by the action of hydroxylamine on dichloro-methylamine[5]:—

$$CH_3{\cdot}NCl_2 + H_2NOH = CH_3{\cdot}N{=}N{\cdot}OH + 2\,HCl = CH_2{<}^{N}_{N} + H_2O + 2\,HCl.$$

The first stage of this reaction is analogous to the formation of diazobenzene hydrate from hydroxylamine and nitrosobenzene:—

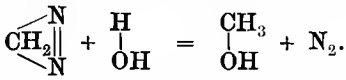
$$\phi{\cdot}N{=}O + H_2NOH = \phi{\cdot}N{=}N{\cdot}OH + H_2O.$$

Diazomethane is an intensely yellow gas. It can be condensed[6] in a freezing mixture of snow and calcium chloride to a yellow liquid boiling below 0°. It

[1] *Ber.* **27**. 1888. [2] *Ber.* **28**. 855 (1895). [3] *Ber.* **35**. 897 (1902).
[4] Thiele, Meyer, *Ber.* **29**. 961 (1896). [5] Bamberger, Renauld, *Ber.* **28**. 1682 (1895).
[6] v. Pechmann, *Ber.* **28**. 855 (1895).

has a violently poisonous action on most people (though some are little affected by it), attacking the eyes and lungs. Chemically it is extremely active. There is obviously a great strain in the ring, which is broken in nearly all its reactions. The normal type of reaction consists in the elimination of the nitrogen and the introduction in its place of two monad groups.

In particular, it reacts with all bodies containing hydroxyl, converting this group into methoxyl: thus with water it gives methyl alcohol:—



In the same way acids are converted into their methyl esters, and phenols into their methyl ethers (anisols).

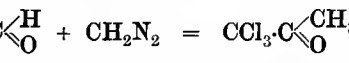
The reactions of some isomeric oximes with diazomethane are peculiar and difficult to explain. We should expect both forms to be converted, and as far as we can see with equal ease, into the two stereoisomeric O-ethers:—

$$R{\cdot}CH{=}NOH + CH_2N_2 = R{\cdot}CH{=}NOCH_3 + N_2.$$

Forster and Dunn[1] have examined the behaviour of the oximes of benzaldehyde, of its three nitro-derivatives, and of its *p*-triazo-derivative, and find it to be quite different from this. The syn-compounds are not acted on at all, except that of *m*-nitro-benzaldehyde, which gives a yield of the O-ether of the anti-compound much larger than that obtained from the anti-compound itself. The anti-oximes are converted to a greater or less extent into their O-ethers. Camphoroxime and benzophenone oxime do not react.

This reaction is of some practical importance for methylation where other methods fail. It has also been used[2] for determining the structure of tautomeric bodies. It has the advantage that it proceeds in the absence of any third body (except ether), generally quantitatively, and at the ordinary temperature; and the only products are the ester or ether and nitrogen. It has, however, been less used for methylation since the discovery of the methyl sulphate method; and recent work has shown that the results obtained in the case of tautomeric substances must be received with caution.

An analogous reaction occurs with aldehydes, which are converted into the corresponding methyl-ketones,[3] e.g.:—



If an acetyl derivative of a phenol is treated with diazomethane, the acetyl group is expelled and the methyl takes its place: for example:—

$$C_6H_3(OEt)_2{\cdot}O{\cdot}CO{\cdot}CH_3 \longrightarrow C_6H_3(OEt)_2{\cdot}OCH_3.$$

(This reaction does not occur in solvents quite free from water, nor if there are other groups present in the ortho position to exert stereo-hindrance.) On the other hand, if the acetyl group is attached to nitrogen (as in acetanilide

[1] *J. C. S.* **1908**. 425.

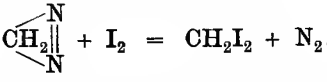
[2] Cf. H. Meyer, *Mon.* **26**. 1311 (*C.* **06**. i. 557) (pyridones); Peratoner, Azzarello, *C.* **06**. i. 1439 (pyridones); Forster, Holmes, *J. C. S.* **1908**. 242 (isonitroso-camphor); Acree, Johnson, Brunel, Shadinger, Nirdlinger, *Ber.* **41**. 3199 (1908) (an elaborate investigation of certain urazoles).

[3] Schlotterbeck. *Ber.* **40**. 479 (1907); **42**. 2559 (1909).

derivatives), it is not expelled under these conditions. Hence the reaction can be used to determine, in the case of acetyl derivatives of aminophenols, whether the acetyl group is attached to oxygen or nitrogen.[1]

With primary and secondary amines, diazomethane forms the methyl derivatives: e.g. with toluidine, methyl-toluidine.

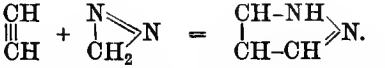
When it is treated with an ethereal solution of iodine the colour disappears at once, with the production of methylene iodide:—



$$CH_2\langle\!\!\rangle N_2 + I_2 = CH_2I_2 + N_2.$$

This reaction is useful for determining the strength of the solution of diazomethane obtained in the preparation. It is titrated with an ethereal solution of iodine of known strength as long as the colour disappears.[2]

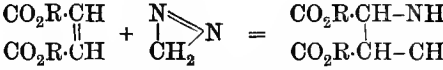
There is also a class of reactions in which the nitrogen is not eliminated. Thus with unsaturated bodies it is capable in many cases of forming addition-compounds. The simplest instance is that if it is left to stand for some time in contact with acetylene, pyrazole is formed, to the extent of 50 per cent. of the theory[3]:—



$$\begin{matrix}CH\\\|\\CH\end{matrix} + \begin{matrix}N\\|\\CH_2\end{matrix}\!\!\rangle N = \begin{matrix}CH\text{–}NH\\|\\CH\text{–}CH\end{matrix}\!\!\rangle N.$$

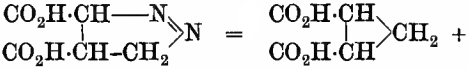
The analogous reaction takes place, but much less easily, with ethylene, giving pyrazoline or dihydropyrazole.[4]

In the same way, but even more readily, diazomethane will combine with unsaturated acids or their esters, having a double or triple bond next to the carboxyl: for example, with fumaric ester it forms the ester of pyrazoline dicarboxylic acid:—



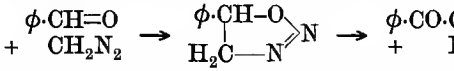
$$\begin{matrix}CO_2R\cdot CH\\\|\\CO_2R\cdot CH\end{matrix} + \begin{matrix}N\\|\\CH_2\end{matrix}\!\!\rangle N = \begin{matrix}CO_2R\cdot CH\text{–}NH\\|\\CO_2R\cdot CH\text{–}CH\end{matrix}\!\!\rangle N.$$

The acids so obtained have the remarkable property of losing their nitrogen when heated alone, giving trimethylene dicarboxylic acids:—



$$\begin{matrix}CO_2H\cdot CH\text{——}N\\|\\CO_2H\cdot CH\text{–}CH_2\end{matrix}\!\!\rangle N = \begin{matrix}CO_2H\cdot CH\\|\\CO_2H\cdot CH\end{matrix}\!\!\rangle CH_2 + N_2.$$

A similar intermediate formation of a nitrogenous ring may probably explain the singular reaction of diazomethane with aldehydes, which have the aldehydic hydrogen replaced by methyl, with the production of ketones[5]:—



$$\begin{matrix}\phi\cdot CH{=}O\\+\quad CH_2N_2\end{matrix} \rightarrow \begin{matrix}\phi\cdot CH\text{–}O\\|\\H_2C\text{—}N\end{matrix}\!\!\rangle N \rightarrow \begin{matrix}\phi\cdot CO\cdot CH_3\\+\qquad N_2\end{matrix}.$$

Of the homologues of diazomethane, Pechmann has prepared diazoethane,

[1] Hertzig, Tichatschek, *Ber.* **39.** 268, 1557 (1906).

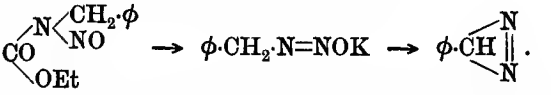
[2] The strength may also be determined by shaking with decinormal hydrochloric acid, and then, after all the diazomethane has been converted into methyl chloride, titrating the excess of acid. H. Meyer, *Mon.* **26.** 1295 (*C.* **06.** i. 555).

[3] v. Pechmann, *Ber.* **31.** 2950 (1898).

[4] Azzarello, *C.* **05.** ii. 1236.

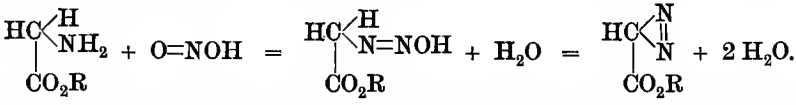
[5] Schlotterbeck, *Ber.* **40.** 479, 3000 (1907); **42.** 2565 (1909).

$C_2H_4N_2$, which closely resembles it. He failed to obtain phenyl-diazomethane by acting on nitroso-benzyl-urethane with alcoholic potash, but Hantzsch,[1] by employing saturated aqueous potash, obtained first the true diazo-hydrate, which, on treatment with water, gave phenyl-diazomethane:—



It is a dark red oil, only slightly volatile; it does not boil without great decomposition, evolving nitrogen and leaving stilbene, $\phi\cdot CH{=}CH\cdot\phi$.

Diazoacetic ester, the first member of the group to be discovered, was obtained by Curtius, in 1883, by the action of potassium nitrite on glycocoll ester hydrochloride:—



It is to be noticed that free glycocoll does not give any diazo-compound with nitrous acid, but goes directly to glycollic acid, with elimination of nitrogen. The whole question of the conditions which determine the reaction of an NH_2 group with nitrous acid is very obscure. The main facts, as far as they are known, are these. Apart from the simple formation of a nitrite, which occurs in some cases, there are three possible reactions. First, the NH_2 group may be replaced by hydroxyl, which is the most frequent case, occurring with all ordinary alkyl-amines and with all amides. Secondly, a true open-chain diazo-compound may be formed, as in the aromatic amines. Thirdly, a ring compound may be produced, a fatty diazo-compound. This last reaction obviously requires that there should be a hydrogen atom on the same carbon atom as the NH_2; if this is absent, as in the aromatic amines, only the first or the second reaction can take place. In fact there are two questions concerned, first, whether an alcohol or an open-chain diazo-compound is the primary product, and secondly, whether the latter, if produced, goes over at once into the ring compound.

As regards the first question, the normal reaction is the production of a hydroxyl compound. The formation of a diazo-compound of any sort seems to depend on the presence of acidic groups in the neighbourhood of the NH_2, though it is by no means all acidic groups which will produce this effect, and in particular it is to be noticed that it does not occur with amides, which are always converted into the acids.

But at any rate those amines which give diazo-compounds are always of a more or less negative character. They comprise in the first place the aromatic amines, in which the NH_2 is attached to the negative benzene nucleus. The only fatty amines which give this reaction are those which contain a carbonyl group, and it would seem that this must be in the α-position to the NH_2, i. e. that the compound must contain the grouping $CO\cdot C\cdot NH_2$. Thus among the amino-acids, Curtius[2] finds that the free acids never form diazo-compounds,

[1] *Ber.* **35.** 897 (1902).

[2] Curtius, Müller, *Ber.* **37.** 1261 (1904). Cf. Angeli, *Ber.* **26.** 1715 (1893).

and of the esters, only those which have the NH_2 in the α-position to the carboxethyl. For example, α-β-diamino-propionic ester gives α-diazo-β-oxy-propionic ester. He has recently shown that the esters of the polypeptides, which have the NH_2 in the same relative position to the carbonyl, can likewise be converted into diazo-compounds :—

$$NH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2Et \rightarrow \begin{matrix} N \\ \| \\ N \end{matrix}\!\!>\!CH{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2Et.$$

Again, the α-amino-ketones, such as amino-acetophenone, $\phi{\cdot}CO{\cdot}CH_2{\cdot}NH_2$, will give diazo-compounds (Angeli), these also containing the grouping $CO{\cdot}C{\cdot}NH_2$. The same rule holds with certain uric acid derivatives such as amino-methyl-uracil,

$$\begin{matrix} NH{-}CO \\ | \quad\ | \\ CO \quad C{\cdot}NH_2, \\ | \quad\ | \\ NH{-}C{\cdot}CH_3 \end{matrix}$$

though this body can only give an open-chain compound, as there is no hydrogen on the carbon carrying the NH_2. On the other hand, the presence of hydroxyl on the carbonyl carbon prevents the formation of diazo-derivatives, as is shown by the behaviour of the free amino-acids. Further, it is found that while the presence of a hydrogen atom on the same carbon as the NH_2 is necessary to the production of a ring diazo-derivative, the stability of this body is greatly increased if there is a second hydrogen atom, i. e. if we start with a body $-CH_2{\cdot}NH_2$ and form a diazo-compound $-CH{:}N_2$. It is possible that this may be due to the body being then able to assume the tautomeric structure $-C\begin{matrix} NH \\ | \\ \| \\ N \end{matrix}$, although, as we shall see later, the supposed evidence for the existence of compounds of this type has been shown to be incorrect.

Diazoacetic ester, $N_2{\cdot}CH{\cdot}CO_2Et$, is a yellow liquid of peculiar smell, boiling at 143°. It does not explode when struck, but does so violently when brought into contact with sulphuric acid. It begins to decompose near its boiling-point into nitrogen and fumaric ester, as phenyl-diazomethane does into nitrogen and stilbene :—

$$\begin{matrix} CO_2R{\cdot}C{-}N \\ \| \quad | \\ CO_2R{\cdot}C{-}N \end{matrix} = 2\,N_2 + \begin{matrix} CO_2R{\cdot}CH \\ \| \\ CO_2R{\cdot}CH \end{matrix}.$$

Its reactions closely resemble those of diazomethane ; thus when boiled with water or dilute acids it liberates nitrogen quantitatively, giving the ester of an oxy-acid :—

$$\begin{matrix} HC{-}N \\ | \quad\ \| \\ CO_2R \quad N \end{matrix} + \begin{matrix} H \\ | \\ OH \end{matrix} = \begin{matrix} HC{-}H \\ | \quad\ | \\ CO_2R \quad OH \end{matrix} + N_2.$$

This reaction has been shown by Bredig and Fraenkel [1] to afford a valuable

[1] Bredig, Fraenkel, *Z. f. Elektrochem.* **11**. 525 (1905); *Ber.* **39**. 1756 (1906); Fraenkel, *Z. Ph. Ch.* **60**. 202 (1907); Bredig, Ripley, *Ber.* **40**. 4015 (1907); Mumm, *Z. Ph. Ch.* **62**. 589 (1908); Holmberg, *Ber.* 41. 1341 (1908).

means of determining the concentration of hydrogen ion, especially at high dilutions. The rate of change was measured by observing the volume of nitrogen evolved, the solution being shaken in a flask connected with a measuring vessel. The reaction is monomolecular, that is, it is proportional to the amount of diazoacetic ester present. It is hastened by the presence of acids. the monomolecular constant being proportional to the concentration of hydrogen ion (with a limit of error of about 3 per cent.) down to N/5,000 concentration of this ion. With weak acids the addition of salts of the acid greatly diminishes the velocity, as we should expect. The addition of alcohol also greatly diminishes it, no doubt by depressing the ionization. On the other hand, when the alcohol is nearly absolute, this effect is reversed, and the addition of traces of water lowers the rate of reaction. Thus with picric acid the addition of 0·18 per cent. of water to absolute alcohol lowers the velocity constant by 22 per cent.; the reaction still continuing to be monomolecular. This anti-catalytic action of water is unexplained[1]; but Goldschmidt and Sunde[2] observed a similar effect on the rate of esterification.

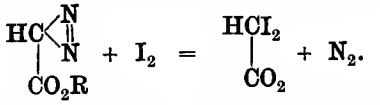
If hydrochloric or sulphuric acid is used to promote the decomposition of the diazoacetic ester, the change gets rapidly slower and finally stops long before the ester has all disappeared. If more acid is added more change takes place, but this again soon comes to an end. This is due to the fact that under these circumstances another reaction takes place, with the production of chloracetic ester:—

$$N_2{\cdot}CH{\cdot}CO_2Et + HCl = Cl{\cdot}CH_2{\cdot}CO_2Et + N_2,$$

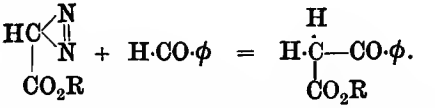
and this removes the catalyst. By determining the amount of chloracetic ester produced, it is possible to calculate the velocities of the two reactions; and it has been shown that the formation of the haloid ester is promoted by the presence of a neutral salt of the acid (e.g. sodium chloride), and that its rate of production is proportional to the concentration of the diazo-ester, to that of the hydrogen ion, and to a function of the concentration of the chlorine ion which could not be exactly determined, but which approximates to the cube root.

The same reaction occurs with nitric, hydrobromic, and hydriodic acids. As regards the three haloid acids, it is found that the proportion of haloid ester produced is greatest *ceteris paribus* with the iodide and least with the chloride, this being the reverse order to that of their tendency to ionization.

When diazoacetic ester is treated with a halogen, it gives the di-halogen-acetic acid:—



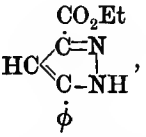
With aldehydes ketonic esters are formed: e.g. with benzaldehyde, benzoyl-acetic ester:—



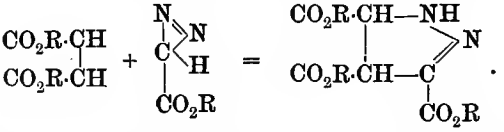
[1] See, however, Lapworth, *J. C. S.* **1908.** 2187; Lapworth, Partington, ib. **1910.** 19.

[2] *Ber.* **39.** 711 (1906).

With bodies containing double or triple links it combines in the same way as diazomethane. Thus it reacts with phenyl-acetylene at 100° to give phenyl pyrazole-carboxylic ester,[1]

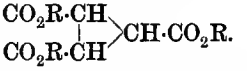


and with unsaturated esters, such as acrylic, cinnamic, and fumaric, it forms various pyrazoline carboxylic esters: e. g. with fumaric ester:—

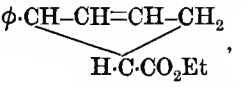


This last body is also produced by the spontaneous decomposition of diazo-acetic ester, if it is allowed to stand for several years exposed to the light, or if it is warmed for a few days; or more rapidly (explosively at 80°) on warming with copper powder.[2] It is obvious that a part of the ester loses nitrogen to form fumaric ester, and this combines with the rest.

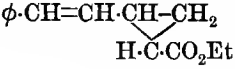
If this product is heated, it loses nitrogen in the normal manner to give trimethylene tricarboxylic ester,



An attempt has been made[3] to use this reaction of diazoacetic ester with unsaturated bodies to test Thiele's theory of double and conjugate links, by treating it with phenyl-butadiene, $\phi\cdot CH{=}CH\cdot CH{=}CH_2$. If addition occurred in the 1,4 positions, as Thiele supposes, the product after the elimination of nitrogen would be a pentamethylene derivative with the formula



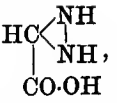
whereas it was found to be a trimethylene compound,



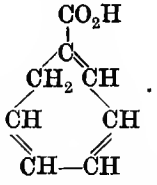
This shows that addition takes place in the 3,4 positions; but as regards its bearing on Thiele's general theory it is to be observed that the intermediate nitrogen-ring compound, in the reaction which actually occurs, contains a 5-ring, whereas 1,4 addition would involve the improbable formation of a 7-ring.

On treatment with ammonia, diazoacetic ester gives under ordinary conditions its amide: but this will be dealt with more fully in discussing the complicated question of its behaviour with alkalies.

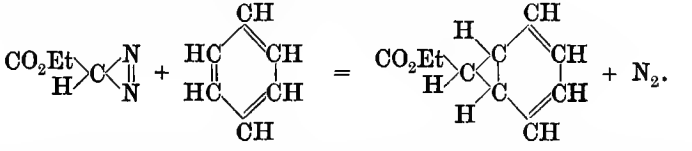
[1] Buchner, *Ber.* **35.** 35 (1902). [2] Silberrad, Roy, *J. C. S.* **1906.** 179.
[3] v. der Heide, *Ber.* **37.** 2101 (1904).

On reduction it first yields hydrazi-acetic acid,  , which, when treated with acids, gives hydrazine and glyoxylic acid, CHO·CO·OH; further reduction converts it into ammonia and glycollic acid.

One of the most remarkable reactions of diazoacetic acid is its behaviour with benzene. This was first discovered by Curtius and Buchner in 1885, and the product has since been investigated by Buchner and his pupils.[1] If diazoacetic ester is heated with a very large excess of benzene, the whole of the nitrogen is evolved, and a body is produced which is isomeric with phenyl-acetic ester, $\phi \cdot CH_2 \cdot CO_2Et$. On saponification the corresponding acid is obtained, which is known as pseudo-phenyl-acetic acid. When the amide of this singular body is boiled with soda it is converted into a heptamethylene derivative, cycloheptatriene carboxylic acid:—



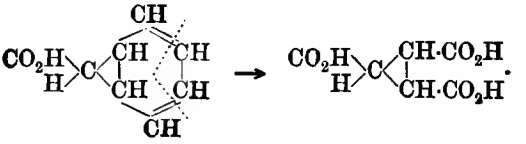
On careful treatment with bromine at 0°, pseudo-phenyl-acetic acid yields a saturated tetrabromide, showing that it contains only two double bonds: hence from its composition it must have two carbon rings. More energetic treatment converts the tetrabromide into an unsaturated cycloheptene acid, which, in order to become saturated, requires to take up two more atoms of bromine or one molecule of hydrobromic acid. It follows from this that pseudo-phenyl-acetic acid must contain a 7-ring, with a bridge link easily broken. On the other hand, it easily passes into a benzene derivative. Its amide is converted by concentrated sulphuric acid into phenyl-acetamide, $\phi \cdot CH_2 \cdot CO \cdot NH_2$, and by oxidation with acid permanganate into benzoic acid. Hence it must contain a 6-ring as well as a 7-ring. This fixes the position of the bridge link. It shows that the $CO_2Et \cdot CH$ residue, which is added on to the benzene by the diazoacetic ester, must attach itself in the ortho position:—



As Buchner has shown, the decompositions of this body afford a very complete proof of its structure. It can theoretically break up, as the formula indicates, in three ways, to give three different forms of ring: a 7-ring (heptamethylene), a benzene ring, or a trimethylene ring. All these three transformations actually occur. Two of them we have seen already: soda converts the body into a 7-ring compound, the isomeric cycloheptatriene carboxylic acid; and

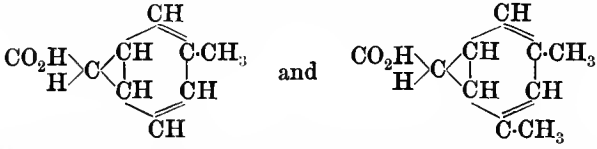
[1] *Ber.* **29.** 106; **30.** 632, 1949; **31.** 399, 402, 2004, 2241, 2247; **32.** 705; **33.** 684, 3453; **34.** 982 (1896–1901).

sulphuric acid breaks the trimethylene ring to give a benzene derivative, also isomeric, namely, ordinary phenyl-acetic acid. Finally, oxidation with acid permanganate breaks the 6-ring, and gives trimethylene tricarboxylic acid :—

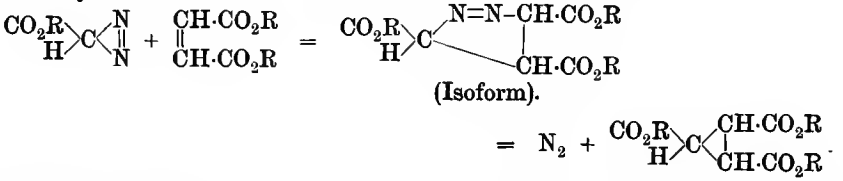


This last reaction enables us to fix with fair certainty the position of the two double bonds in pseudo-phenyl-acetic acid. They always form the point of attack when an unsaturated body is oxidized ; and the fact that in this reaction two carboxyls—that is to say, two carbon atoms—remain attached to the trimethylene ring, shows fairly conclusively that these two carbon atoms must be attached only by single bonds in the original acid. That is to say, the formula of pseudo-phenyl-acetic acid is what it is assumed to be in the above equation.

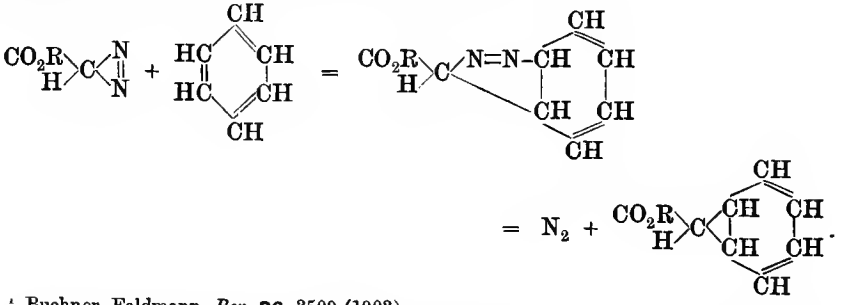
In a similar manner diazoacetic ester combines with toluene[1] and with meta-xylene,[2] giving compounds whose formulae have been shown to be



The formation of these substances is of interest from the point of view of the benzene theory. The reaction is really precisely similar to that which occurs between diazoacetic ester and the esters of unsaturated acids. Thus, as we have seen, it reacts with fumaric ester to give an addition-product—pyrazoline tricarboxylic ester—and this on heating loses nitrogen to form trimethylene tricarboxylic ester :—



In exactly the same way we can write the reaction with benzene, using Kekulé's formula :—

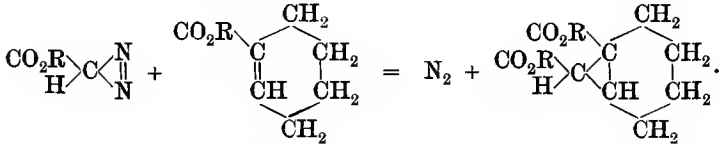


[1] Buchner, Feldmann, *Ber.* **36.** 3509 (1903).

[2] Buchner, Delbrück, *Ann.* **358.** i. (1908). This paper affords a remarkably ingenious and complete example of the way in which the structure of such compounds can be established.

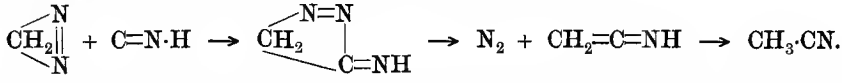
That is, the benzene (and similarly toluene and xylene) behaves as though it had three ordinary double links. The reaction occurs at a higher temperature than with the unsaturated esters, and the (hypothetical) intermediate pyrazoline derivative must be supposed to be unstable at this temperature and to break up as fast as it is formed.

A still closer analogy is the condensation of diazoacetic ester with Δ^1-tetrahydro-benzoic ester, which undoubtedly contains an ordinary double link, the product being the carboxylic ester of the saturated tetrahydro-pseudo-phenylacetic ester:—



Of course this reaction is no argument against Thiele's benzene theory, which in fact does ascribe three double links to benzene, though it goes further and explains the peculiarities of their behaviour.

It may be pointed out here that the occurrence of a cycle of reactions of this kind—the formation of a nitrogenous ring followed by the elimination of the nitrogen—throws doubt in some cases on the validity of the arguments as to the structure of tautomeric bodies derived from their reactions with fatty diazo-compounds. For example, the formation of acetonitrile from diazomethane and prussic acid, which was assumed to be evidence of the nitrile formula, can equally well be explained on the imide formula thus:—



This particular reaction has lost its importance since it has been found that methyl isocyanide is actually produced along with acetonitrile; but the example is sufficient to show that a certain amount of caution is required in interpreting the evidence in such cases.

Another important series of reactions of diazoacetic ester are its polymerizations with alkalies. This subject has had a singular history. The phenomenon was first observed by Curtius,[1] and led him to the discovery of hydrazine and so of hydrazoic acid. He regarded the products as triple polymers of the original ester, and called them triazo-compounds. They were then reinvestigated by Hantzsch and Silberrad,[2] who showed that their molecular weight was not three times but twice that of the diazo-ester; they characterized many of the more important products, and suggested formulae for them. The work has recently been revised by Curtius, Darapsky, and Müller,[3] who have greatly

[1] *Ber.* **18.** 1283; *J. pr. Ch.* [2] **38.** 408 (1888). Cf. Traube, *Ber.* **29.** 669 (1896).

[2] *Ber.* **33.** 58 (1900); Silberrad, *J. C. S.* **1902.** 598.

[3] Curtius, Thompson, *Ber.* **39.** 1383, 3398, 4140; Curtius, Darapsky, Müller, *Ber.* **39.** 3410, 3776 (1906); **40.** 84, 815, 1176, 1194, 1470 (1907); **41.** 3140, 3161 (1908). The last of these papers contains a summary of the whole subject. Cf. E. Müller, *Ber.* **41.** 3116; Bülow, *Ber.* **39.** 2618, 4106.

extended our knowledge of these compounds, and have shown that the conclusions of Hantzsch and Silberrad are in many points incorrect. The present state of the subject is as follows:—

If diazoacetic ester is treated in the cold with dilute alkali or dilute ammonia, it is converted in the usual way into the potassium salt or the amide of diazoacetic acid, $\begin{matrix}N\\ \|\\ N\end{matrix}\!\!>\!CH\cdot COOK$ or $\begin{matrix}N\\ \|\\ N\end{matrix}\!\!>\!CH\cdot CO\cdot NH_2$. Free diazoacetic acid is too unstable to exist, and decomposes as soon as it is liberated. If diazoacetamide is warmed with alkali, it undergoes a remarkable isomeric change into a triazolone:—

$$\begin{matrix}N{=}N\\ |\quad\diagdown NH_2\\ CH{-}CO\end{matrix} \longrightarrow \begin{matrix}N{=\!=}N\\ |\quad\diagup NH.\\ CH_2{-}CO\end{matrix}$$

On hydrolysis this body breaks up, as does diazoacetamide itself, into nitrogen, ammonia, and glycollic acid.

If diazoacetic ester is treated in the cold with concentrated potash or liquid ammonia, it gives the amide or the potassium salt of the so-called pseudo-diazoacetic acid, a double polymer (incapable of existence in the free state) which can be shown to be a dihydro-tetrazine of the formula:—

$$COOH\cdot C\begin{matrix}N{-}NH\\ \diagdown\quad\diagup\\ N{=}N\end{matrix}CH\cdot COOH.$$

The same reaction occurs with primary amines; but secondary amines react more slowly and form derivatives of another series of tetrazine derivatives, the bis-diazo-compounds, which will be mentioned below.

The alkaline alcoholates act on diazoacetic ester to give yellow very unstable ester-salts, which Hantzsch and Lehmann[1] regarded as isodiazo-compounds, e.g. $CO_2Et\cdot C\begin{matrix}N\cdot K\\ \diagdown\quad\diagup\\ N\end{matrix}$. Curtius[2] and his collaborators have, however, proved from their decomposition-products that they are tetrazine derivatives, probably belonging to the pseudo-diazo series. The only true salt of diazoacetic ester known is that of mercury,[3] which almost certainly has the metal attached to carbon:—

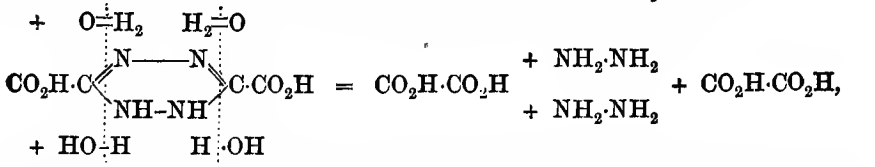
$$CO_2Et\cdot\begin{matrix}C\cdot hg\\ \diagdown\quad\diagup\\ N\end{matrix}\!\!\|\,N.$$

On the other hand, if diazoacetic ester is heated with concentrated potash or strong ammonia, the salt or amide of an isomeric dihydro-tetrazine derivative is formed, known as bis-diazoacetic acid (the original triazo-compound of Curtius): it may have either of two structures:—

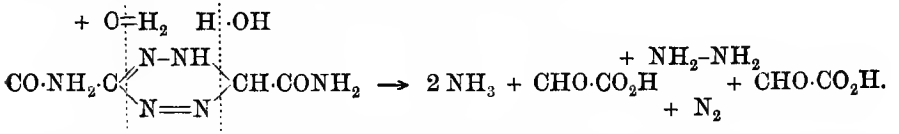
$$CO_2H\cdot C\begin{matrix}N{-\!-\!-}N\\ \diagdown\quad\diagup\\ NH{-}NH\end{matrix}C\cdot CO_2H \quad\text{or}\quad CO_2H\cdot C\begin{matrix}N{-\!-}NH\\ \diagdown\quad\diagup\\ NH{-}N\end{matrix}C\cdot CO_2H.$$

[1] *Ber.* **34**. 2506 (1901). [2] *Ber.* **41**. 3140 (1908).
[3] Buchner, *Ber.* **28**. 215 (1895).

The structure of these 6-ring compounds is determined mainly by their behaviour on hydrolysis. Under these circumstances the grouping =N–N= always breaks off as hydrazine, and –N=N– as nitrogen. Thus bis-diazoacetic acid is hydrolysed to two molecules each of oxalic acid and hydrazine :—

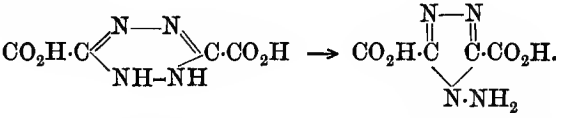


while pseudo-diazoacetamide ultimately gives two molecules of ammonia, two of glyoxylic acid, one of nitrogen, and one of hydrazine :—

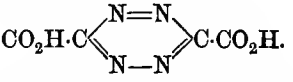


The bis-diazo series may be obtained from the pseudo-diazo-compounds by further treatment with potash. The change is exactly analogous to that of an azo-compound into the isomeric hydrazone.

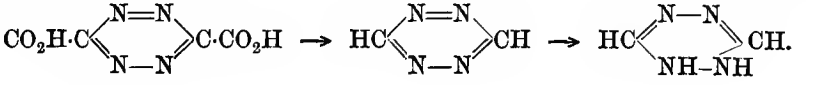
If the bis-diazo-compounds are further heated with excessively concentrated potash, one of the nitrogen atoms is extruded from the ring, and a triazole derivative is formed :—



On oxidation, both the pseudo-diazo- and the bis-diazo-series are converted into derivatives of tetrazine dicarboxylic acid :—

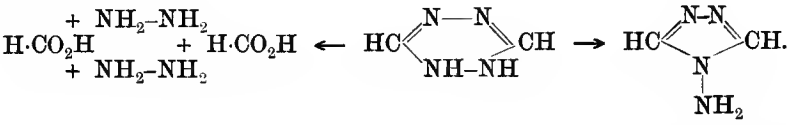


We should expect to find that these 6-ring derivatives could be made to lose the carboxyl groups and yield the simple ring compounds. Hantzsch and Silberrad considered that they had done this, but the bodies they obtained were really triazoles. Thus bis-diazoacetic acid loses two carboxyls on heating, giving 1-N-amino-3,4-triazole.[1] Pseudo-diazoacetic acid cannot be isolated, so in this case the reaction is impossible. It is, however, possible in an indirect way to obtain the dihydro-tetrazine which is the real bis-diazomethane.[2] If the tetrazine dicarboxylic acid (the oxidation-product whose formula is given above) is heated, it loses its carboxyls and gives the free tetrazine, a deep red solid: and this on reduction is converted into the dihydro-tetrazine which is the mother substance of the bis-diazo series :—

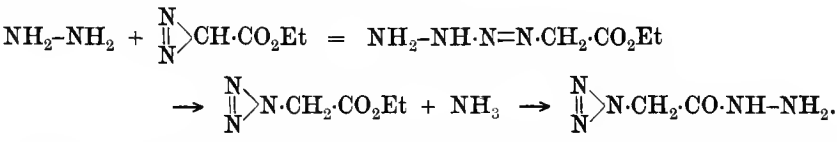


[1] Bülow, *Ber.* **39**. 2618, 4106 (1906). [2] *Ber.* **40**. 84, 836 (1907).

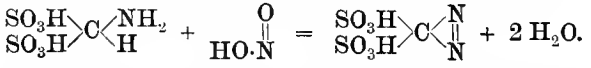
Its structure is shown by its giving formic acid and hydrazine (and no nitrogen) on hydrolysis. It exhibits the characteristic tendency of these 6-rings to 'crumple', with the formation of a 5-ring, being converted by gentle warming into an amino-triazole:—



We have thus seen how the 3-ring of diazoacetic ester can be converted into a 5-ring (triazole), and into two different forms of a 6-ring (dihydro-tetrazine). There is yet another change possible. If diazoacetic ester is treated with hydrazine, an N_3-ring is formed, the product being the hydrazide of azido-acetic acid.[1] This singular reaction is most easily explained by the intermediate production of a 'buzylene' derivative:—



There is another method of preparing diazomethane derivatives due to v. Pechmann, which may be mentioned on account of its simplicity. Sulphurous acid condenses with hydrocyanic acid (one molecule of the latter to two of the former) to give a disulphonic acid, which can be shown to be a primary amine: for example, by its giving Hofmann's test with chloroform and potash. It must, therefore, be aminomethane disulphonic acid, $\begin{matrix}SO_3H\\SO_3H\end{matrix}\!\!>\!C\!<\!\begin{matrix}NH_2\\H\end{matrix}$. When this is treated with nitrous acid it forms diazomethane disulphonic acid:—



This body shows all the reactions of fatty diazo-compounds: for example, with iodine it gives nitrogen and diiodo-methane disulphonic acid, so that there can be no doubt about its constitution. It is to be noticed that we have here the case of a fatty compound which is capable of being diazotized although it does not contain the group $CO{\cdot}C{\cdot}NH_2$. But it has a very similar structure. It contains an NH_2 in the α-position to a strongly negative group, namely, the SO_3H. It is also to be observed that in this case the free acid can be diazotized, whereas the amino-carboxylic acids must first be converted into their esters.

The body is further interesting as providing a practical method of making hydrazine. It forms a direct addition-compound with another molecule of sulphurous acid, of the formula $\begin{matrix}SO_3H\\SO_3H\end{matrix}\!\!>\!C\!<\!\begin{matrix}N{\cdot}H\\N{\cdot}SO_3H\end{matrix}$, and this when boiled with acids splits up with the formation of hydrazine.

[1] *Ber.* **41.** 344 (1908).

III. N_3 GROUP. AZIDES

The azides, otherwise known as azimido- or triazo-compounds, or as diazoimides, are the esters of hydrazoic acid or azoimide, $H{\cdot}N\langle{}^{N}_{\|}{}^{N}$. The number which is theoretically possible is limited, from the fact that the ring is only monovalent; but considerable attention has been directed to them in recent years.

They were first prepared by Griess, by the action of ammonia on the diazoperbromides:—

$$\phi{\cdot}\overset{\|}{N}{\cdot}Br_3 + H_3N = \phi{\cdot}N\langle{}^{N}_{\|}{}^{N} + 3\,HBr.$$

They may also be formed by treating the diazo-compounds with hydrazoic acid, a reaction resembling Sandmeyer's:—

$$\phi{\cdot}N_2{\cdot}OH + HN_3 = \phi{\cdot}N_3 + N_2 + H_2O,$$

and further, in an unexpected way, by the action of the diazo-compounds on hydroxylamine,[1] possibly through the nitrosamine:—

$$\phi{\cdot}NH{\cdot}NO + H_2N{\cdot}OH \longrightarrow \phi{\cdot}NH{\cdot}N{=}N{\cdot}OH \longrightarrow \phi{\cdot}N\langle{}^{N}_{\|}{}^{N} + H_2O.$$

Another method, which is most convenient for preparing them on a large scale, is by the action of nitrous acid on hydrazine derivatives. An intermediate product, a nitrosohydrazine, is formed first, which can in many cases be isolated by working at a low temperature. This method is particularly used in preparing the azides of acids, and is part of the cycle of changes by which Curtius prepares hydrazoic acid from hydrazine:—

$$\begin{matrix}\phi{\cdot}CO{\cdot}NH{-}NH_2\\ +\quad HO{\cdot}NO\end{matrix} = H_2O + \phi{\cdot}CO{\cdot}N\langle{}^{NH_2}_{NO} = 2\,H_2O + \phi{\cdot}CO{\cdot}N\langle{}^{N}_{\|}{}^{N}.$$

Curtius's method of making hydrazoic acid consists in starting with an amide insoluble in alcohol—he generally uses hippuramide—and treating it with hydrazine hydrate, whereby it is converted into the acid hydrazide. This is then transformed into the acid azide as above, and the azide dissolved in alcohol and treated with ammonia, which reproduces the original amide, and, as it is insoluble in alcohol, precipitates it; while the hydrazoic acid remains in solution:—

$$R{\cdot}CO{\cdot}N_3 + NH_3 = R{\cdot}CO{\cdot}NH_2 + HN_3.$$

In the same way phenyl azide, $\phi{\cdot}N_3$, is best made by acting on phenyl hydrazine with nitrous acid.[2]

The simplest organic azide, methyl azide, $CH_3{\cdot}N_3$, was discovered by Dimroth and W. Wislicenus,[3] who made it by dissolving sodium azide, formed by the action of nitrous oxide on sodamide, in water, and treating it with methyl sulphate:—

$$2\,NaN_3 + (CH_3)_2SO_4 = Na_2SO_4 + 2\,CH_3N_3.$$

[1] E. Fischer, *Ann.* **190.** 96 (1877); Mai, *Ber.* **25.** 372 (1892).

[2] Dimroth, *Ber.* **35.** 1029 (1902). [3] *Ber.* **38.** 1573 (1905).

The methyl azide is evolved as a gas and condensed in a freezing mixture, a yield of over 80 per cent. being obtained. It is a colourless liquid, boiling at 20–21°, and has an ethereal but unpleasant odour, resembling that of azoimide itself. The authors say that in great dilution the vapour smells like the air of a mouldy cellar. It explodes violently when brought into a flame, but its temperature of explosion is high, over 500°, so that it was found possible to determine its vapour density, which is normal, and even to analyse it completely by combustion, by mixing its vapour with a large excess of air or carbon dioxide.

Several azido-derivatives of the simpler fatty compounds, such as azido-acetic acid, $N_3 \cdot CH_2 \cdot CO_2H$, and azido-acetone, $N_3 \cdot CH_2 \cdot CO \cdot CH_3$, have been prepared by acting with sodium azide on the corresponding halogen derivatives. They are colourless liquids or solids of low melting-point, which, though they explode on heating, are fairly stable.

The aromatic azides, like diazobenzene-imide or phenyl azide, $\phi \cdot N_3$, are oily or crystalline substances of a strong peculiar smell, which explode at a somewhat high temperature. On boiling with dilute sulphuric acid they evolve nitrogen and form aminophenols. This is no doubt due to the primary production of phenyl-hydroxylamine :—

$$\phi \cdot N\langle \overset{N}{\underset{N}{\|}} + \overset{H}{|}OH = N_2 + \phi \cdot N\langle \overset{H}{OH} \rightarrow C_6H_4\langle \overset{OH}{NH_2} :$$

so that the reaction is exactly similar to that of the fatty diazo-compounds with dilute acids :—

$$CH_2\langle \overset{N}{\underset{N}{\|}} + \overset{H}{|}OH = CH_2\langle \overset{H}{OH} + N_2.$$

The evolution of nitrogen on treatment with either acid or alkali is a general reaction of the azides; but in the case of many of the fatty derivatives the ultimate product is a ketone-imine, which easily loses ammonia to form the ketone or aldehyde: for example, camphoryl azide[1] or azido-acetone :—

$$CH_3 \cdot CO \cdot CH_2 \cdot N_3 \rightarrow CH_3 \cdot CO \cdot CH{=}NH \rightarrow CH_3 \cdot CO \cdot CH{=}O.$$

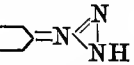
On the other hand, many azides when treated with alkali undergo a different reaction, the whole azide group being eliminated as hydrazoic acid. In the aromatic compounds this reaction is promoted by the presence of negative groups on the ring: thus when dinitrophenyl azide, $(NO_2)_2C_6H_3 \cdot N_3$, is boiled with alcoholic potash it is converted into potassium azide and dinitrophenol. This may be compared to the weakening of the attachment of chlorine to the nucleus by negative groups; indeed this is only one of many points of resemblance between the N_3 group and the halogens. Among the fatty compounds the relations are more complicated.[2] Camphoryl azoimide is hydrolysed by potash to nitrogen and the amide; but the simpler fatty compounds, such as azidoacetic ester and azido-acetone and its oxime, all of which contain the group $N_3 \cdot CH_2 \cdot CO$, give at the same time a considerable amount of free azoimide.

[1] Forster, Fierz, *J. C. S.* **1905**. 826.

[2] Forster, Fierz, *J. C. S.* **1905**. 722, 826; **1908**. 1174, 1859; Forster, ib. **1909**. 184, 191.

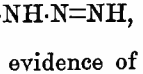
The behaviour of the two isomeric derivatives of propionic ester is peculiar. The α-compound, $CH_3{\cdot}CH_2N_3{\cdot}CO_2Et$, is very stable, and when the N_3 ring is attacked it gives nitrogen and no azoimide; while the β-compound,

$$CH_2N_3{\cdot}CH_2{\cdot}CO_2Et,$$

splits off azoimide with great ease. It is possible that these differences are connected with the readiness with which the bodies are able to go over into a tautomeric enolic form. A similar change is indicated by the behaviour of para-azido-phenol,[1] $N_3{\cdot}C_6H_4{\cdot}OH$. Whereas the corresponding ortho and meta compounds are colourless substances, existing only in one form, the para body occurs in two forms, one colourless, the other blue; and these differences are maintained in solution. The blue form may be a quinoid derivative of the structure  ; but there is no evidence of this.

Various attempts have been made to reduce the azides, but in all cases these resulted in breaking up the molecule, until recently Dimroth [2] was successful in obtaining a direct reduction-product of phenyl azide, with very remarkable properties. He used a solution of stannous chloride in ether containing hydrochloric acid, which has the advantage that the product is precipitated in the form of its tin double salt. If phenyl azide is reduced in this way at $-18°$, it takes up two atoms of hydrogen, and yields a very unstable substance, to which we may provisionally give the formula of phenyl-triazene, $\phi{\cdot}N{=}N{\cdot}NH_2$. Like the other triazenes this forms metallic derivatives, the copper salt being fairly stable, and the silver salt spontaneously explosive. Phenyl-triazene forms colourless plates which melt at 50°, but rapidly decompose, even in the cold, in contact with a trace of any solvent, giving aniline and nitrogen:—

$$\phi{\cdot}N{=}N{\cdot}NH_2 \;=\; \phi{\cdot}NH_2 + N_2.$$

If these crystals are filtered off and placed on a porous tile under the microscope, they begin in a very few minutes to break up into small fragments, many of which are thrown up into the air. In about five minutes the crystalline plates are converted into a fine powder, which soon begins to decompose into aniline and nitrogen. This powder is an isomer, melting at 40°, which is reconverted into the original plates (M. Pt. 50°) by recrystallization from ether. It must be an isomer, because its formation is practically unaccompanied by loss of weight; hence its production cannot be due to the loss of ether of crystallization. It cannot be a mere case of physical dimorphism, because the more stable form has the lower melting-point. The two must therefore be chemical isomers, and there are various possible formulae: $\phi{\cdot}N{=}N{\cdot}NH_2$ (syn- and anti-), $\phi{\cdot}NH{\cdot}N{=}NH$, and also a ring structure,  , phenyl cyclo-triazane. No evidence of differences in chemical behaviour between the two forms has yet been obtained, but the general reactions of the body point clearly to two structures, that of a triazene and that of a cyclo-triazane. It condenses with phenyl isocyanate to form a urea, $\phi{\cdot}N{=}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}\phi$, this being the normal behaviour of the triazenes, as we have seen, so that we should infer that

[1] Forster, Fierz, *J. C. S.* **1907**. 855, 1350. [2] *Ber.* **40**. 2376 (1907).

it had one of the first two formulae given above; while on oxidation it is reconverted quantitatively into phenyl azide, which points to its being the ring compound $\phi\cdot N\langle\begin{smallmatrix}NH\\|\\NH\end{smallmatrix}$. It is at least probable that these two formulae represent the two isomeric forms.

This tautomerism of the derivatives of triazene and those of cyclotriazane:—

$$HN{=}N\cdot NH_2 \rightleftharpoons HN\langle\begin{smallmatrix}NH\\|\\NH\end{smallmatrix},$$

is of great interest. It serves to explain, for example, the fact[1] that phenyl semicarbazide cannot be made in the Hofmann reaction to go into phenyltriazene, but phenyl azide is obtained instead. The triazene which is no doubt first produced changes into the ring compound, and this is then oxidized by the hypobromite:—

$$CO\langle\begin{smallmatrix}NH\cdot NH\cdot\phi\\NH_2\end{smallmatrix} \rightarrow H_2N\cdot NH\cdot NH\cdot\phi \rightarrow H_2N\cdot N{=}N\cdot\phi \rightarrow \begin{smallmatrix}HN\\|\\HN\end{smallmatrix}\rangle N\cdot\phi \rightarrow \begin{smallmatrix}N\\\|\\N\end{smallmatrix}\rangle N\cdot\phi.$$

Dimroth has shown[2] that phenyl azide can be used for several important syntheses, some of which have already been mentioned. It condenses with bodies containing an acidic methylene group, such as acetoacetic and malonic esters, in presence of sodium ethylate, in somewhat the same way as diazomethane does with doubly linked compounds, except that in this case water or alcohol is eliminated. The N_3 ring is broken unsymmetrically, and the residue joins on to two contiguous carbons of the ester to give a derivative of a 1,2,3-triazole, a ring containing three consecutive nitrogen atoms and two carbons. It is very probable that a diazoamino-compound (triazene) is formed as an intermediate product[3]: for example, with malonic ester:—

$$\phi\cdot N\langle\begin{smallmatrix}N{=}N\\\end{smallmatrix} + \begin{smallmatrix}CH_2\cdot CO_2Et\\|\\CO\cdot OEt\end{smallmatrix} = \phi\cdot NH\begin{smallmatrix}N{=}N\cdot CH\cdot CO\cdot OEt\\|\\EtO\cdot CO\end{smallmatrix}$$

$$= \phi\cdot N\langle\begin{smallmatrix}N{=}N\\|\\CO{-}CH\cdot CO\cdot OEt\end{smallmatrix} + EtOH.$$

The product in this case is of especial interest from the fact that it occurs in two distinct desmotropic forms.[4] The keto-form, whose structure is given above, is a neutral substance, while the enol:—

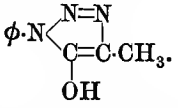
$$\phi\cdot N\langle\begin{smallmatrix}N{=}N\\|\\C{=}C\cdot CO\cdot OEt,\\|\\OH\end{smallmatrix}$$

is an acid strong enough to be titrated with phenol phthalein. The two can be converted into one another, and their desmotropy is repeated throughout the whole

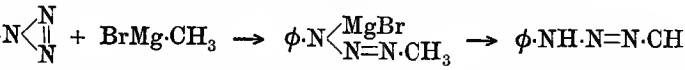
[1] Darapsky, *Ber.* **40.** 3033 (1907).
[2] *Ber.* **35.** 1029, 4041 (1902); **36.** 909 (1903); **38.** 670 (1905).
[3] Dimroth, Frisoni, Marshall, *Ber.* **39.** 3920 (1906).
[4] Dimroth, *Ann.* **335.** 1 (1904); **338.** 143 (1905).

series of their derivatives, including the free acids (of which the keto- is monobasic and the enol dibasic) and their salts.

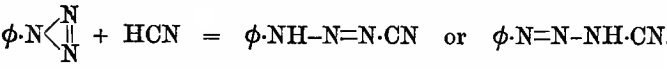
It is remarkable that this condensation with the azides is not confined to compounds with an acidic methylene group, but also occurs, for example, with acetic and propionic esters, in which the methylene is only attached on one side to a negative group, and is not generally regarded as having acidic properties. Thus propionic ester forms a compound:—



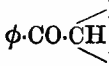
Another synthesis which Dimroth has carried out by means of the azides is that of the fatty and the mixed diazoamino-compounds, as has already been described, by condensation with Grignard's reagent:—

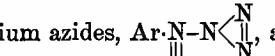
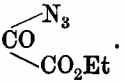


The same opening of the N_3 ring, with the production of a diazoamino-compound, occurs under the influence of hydrocyanic acid, as we have already seen in dealing with the so-called diazoguanidine (carbamide-imide-azide). Phenyl azide undergoes the same change when treated with hydrocyanic acid[1]:—



The second formula is the more probable, but of course the two are desmotropic.

It is to be noticed[2] that one at least of the fatty diazo-compounds, diazoacetophenone,  , behaves in the same way, and gives with prussic acid an open-chain diazo-cyanide, $\phi\cdot CO\cdot CH_2\cdot N{=}N\cdot CN$.

The diazonium azides,  , are worth noticing from the very singular group of five nitrogen atoms which they contain. They have been prepared by Hantzsch[3] by treating the anti-diazo-hydrates with certain azide derivatives, such as azido-carbonic ester,  . They are crystalline substances, soluble in water, insoluble in ether, which are violently explosive, and are decomposed by soda to a diazotate and sodium azide.

[1] Wolff, Lindenhayn, *Ber.* **37**. 2374 (1904). [2] Wolff, *Ann.* **325**. 129 (1902).
[3] *Ber.* **36**. 2056 (1903).

IV. 4-RINGS

Of the 4-rings which contain nitrogen very little is known. We have, however, an example of a C_3N ring in *trimethylene imine*, which is made in the following way. The amide of toluene-*p*-sulphonic acid condenses with trimethylene bromide to give the trimethylene-imide:—

$$CH_3{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH_2 + \begin{matrix} Br{\cdot}CH_2 \\ \\ Br{\cdot}CH_2 \end{matrix}\!\!>\!CH_2 = CH_3{\cdot}C_6H_4{\cdot}SO_2{\cdot}N\!<\!\begin{matrix} CH_2 \\ \\ CH_2 \end{matrix}\!\!>\!CH_2 + 2\,HBr.$$

The decomposition of the imide is not easy. The imine required would be at once decomposed by acids, and it is necessary to treat the compound with sodium in boiling amyl alcohol solution. The nascent hydrogen splits off the imine, on which it has no further action, and reduces the sulphonic acid to toluene and sulphurous acid.

Trimethylene imine[1] is a liquid boiling at 63°, which fumes in the air and smells strongly of ammonia. In fact it closely resembles ethylene imine, and not least in the remarkable ease with which the ring is opened.[2] Acids break it at once. Even on evaporating the solution of the hydrochloride considerable decomposition occurs. Hydrochloric acid merely adds itself on to form chloropropylamine, $CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$. With sulphuric acid water is taken up, giving oxypropylamine, $CH_2OH{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$. The fact that the body really is trimethylene imine, and not the isomeric propylene-amine, is shown by its giving with nitrous acid a nitroso-derivative, $\begin{matrix} CH_2{-}CH_2 \\ | \quad\; | \\ CH_2{-}N{\cdot}NO \end{matrix}$, which proves it to be a secondary base.

We may consider here the question of the stability of the polymethylene imines, bodies of the general formula $(CH_2)_nNH$. They are commonly formed either by loss of ammonium chloride from the hydrochloride of the corresponding diamine:—

$$(CH_2)_n\!<\!\begin{matrix} NH_2 \\ NH_2{\cdot}HCl \end{matrix} \longrightarrow (CH_2)_n\!>\!NH + NH_4Cl\,;$$

or by loss of hydrochloric acid from the chloramine:—

$$(CH_2)_n\!<\!\begin{matrix} Cl \\ NH_2 \end{matrix} \longrightarrow (CH_2)_n\!>\!NH + HCl.$$

The readiness with which they are formed increases[3] from the ethylene compound up to the tetramethylene compound (tetrahydro-pyrrol or pyrrolidine). The pentamethylene derivative is easily produced, but less so than the tetra-[4], in accordance with the usual rule that the 5-ring is the most stable. As regards the higher members of the series, though these have been described up to decamethylene imine, it is probable that they have not the structures assigned to them. Hexamethylene-diamine (and its chloramine) seems to form a small quantity of the corresponding imine, derivatives of which undoubtedly exist, as will be shown later, but the heptamethylene compound goes entirely to other

[1] Howard, Marckwald, *Ber.* **32**. 2036 (1899).
[2] Cf. Gabriel, Colman, *Ber.* **39**. 2889 (1906).
[3] Cf. v. Braun, Steindorff, *Ber.* **38**. 3083 (1905).
[4] Cf. Willstätter, *Ber.* **33**. 365 (1900).

products,[1] and the same is the case with the 8- and 10-carbon analogues. These products are in some cases probably polymers of the type of piperazine, $HN\langle^{(CH_2)_n}_{(CH_2)_n}\rangle NH$ (in which the larger rings seem to be more stable),[2] while in other cases the ring closes up through a carbon atom which is not at the other end of the chain. Thus Blaise and Houillon[3] have shown that the product obtained on heating octomethylene-diamine, $NH_2{\cdot}(CH_2)_8{\cdot}NH_2$, is not octomethylene imine but mainly *α-n*-butyl-pyrrolidine,

$$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}\underset{\displaystyle NH}{\overset{\displaystyle CH_2-CH_2}{\overset{|}{CH}\quad\overset{|}{CH_2}}},$$

and that the supposed decamethylene imine of Krafft[4] is really hexyl-pyrrolidine.

The derivatives of hexamethylene imine have been obtained in a different way, and identified beyond doubt, by Gabriel.[5] Methyl-ε-aminoamyl ketone loses water to form a base, $C_7H_{13}N$, presumably in this way :—

$$\begin{matrix} CH_3 \\ | \\ HO{\cdot}C{=}CH-CH_2 \\ | \\ H_2N{\cdot}CH_2-CH_2-CH_2 \end{matrix} \rightarrow \begin{matrix} CH_3 \\ | \\ C{=}CH-CH_2 \\ / \quad | \\ HN \quad CH_2-CH_2-CH_2 \end{matrix}.$$

If this body is reduced (or if the ketone is reduced, when water is split off at the same time) it gives the saturated 7-ring imine, methyl-hexamethylene imine :-

$$\begin{matrix} CH_3 \\ | \\ CH-CH_2-CH_2 \\ / \quad | \\ HN \quad CH_2-CH_2-CH_2 \end{matrix}.$$

The only other formulae that this body might possess are those of ethyl-piperidine, propyl-pyrrolidine, or of the corresponding derivatives of trimethylene or ethylene imine. The last two are excluded, since hydrochloric acid, which would break their rings, has no action on this body. The ethyl-piperidine and the propyl-pyrrolidine in question are known, and are quite different substances. There can thus be no doubt that the substance is really a 7-ring imine, of the constitution which Gabriel assigns to it.

In connexion with the formation of these imine rings a remarkable case of stereo-hindrance has been observed.[6] The 1,4- and 1,5-dibromides, such as *o*-xylylene bromide and 1,4- and 1,5-dibromopentane, condense with primary aromatic amines to form phenyl-imines :—

$$CH_2\langle^{CH_2{\cdot}CH_2{\cdot}Br}_{CH_2{\cdot}CH_2{\cdot}Br} + H_2N{\cdot}\phi = CH_2\langle^{CH_2{\cdot}CH_2}_{CH_2{\cdot}CH_2}\rangle N{\cdot}\phi + 2\,HBr.$$

Substituted amines behave in the same way, if their substituents are in the

[1] v. Braun, C. Müller, *Ber.* **38.** 2203 (1905); **39.** 4110 (1906).

[2] Howard, Marckwald, *Ber.* **32.** 2038 (1899). Cf. v. Braun, *Ber.* **39.** 4347 (1906).

[3] *C. R.* **142.** 1541 (*C.* **06.** ii. 527).

[4] Krafft, Phookan, *Ber.* **25.** 2252 (1892); Krafft, *Ber.* **39.** 2193 (1906).

[5] *Ber.* **42.** 1259 (1909).

[6] Scholtz, *Ber.* **31.** 414, 627, 1154, 1707 (1898); Scholtz, Friemehlt, *Ber.* **32.** 848 (1899) Scholtz, Wassermann, *Ber.* **40.** 852 (1907).

meta or para position. But if they have a substituent in the ortho position to the NH_2, the reaction takes a different course, and an open-chain compound is formed: for example, with ortho-toluidine:—

$$CH_2\begin{matrix}\nearrow CH_2\cdot CH_2\cdot NH\cdot C_6H_4\cdot CH_3\\ \searrow CH_2\cdot CH_2\cdot NH\cdot C_6H_4\cdot CH_3\end{matrix}.$$

In this reaction α-naphthylamine behaves as an ortho-substituted compound, while β-naphthylamine does not. In the case of one di-ortho-substituted compound which was investigated (mesidine) no reaction was obtained at all.

A compound containing a C_2N_2 ring is Curtius's *dimethyl-aziethane*,[1] obtained by the condensation of hydrazine with diacetyl in molecular proportions:—

$$\begin{matrix}CH_3\cdot CO\\ CH_3\cdot CO\end{matrix} + \begin{matrix}H_2N\\ H_2N\end{matrix} = \begin{matrix}CH_3\cdot C{=}N\\ CH_3\cdot C{=}N\end{matrix} + 2\,H_2O.$$

It is a crystalline powder, melting at 270°.

[1] Curtius, Thun, *J. pr. Ch.* [2] **44.** 175 (1891).

CHAPTER XVII

5-RINGS

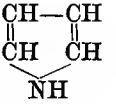
Of the great variety of 5-ring compounds which have been investigated, only one class will be dealt with: those containing a ring of four carbon atoms and one nitrogen. This includes the pyrrol and the indigo derivatives.

PYRROL GROUP[1]

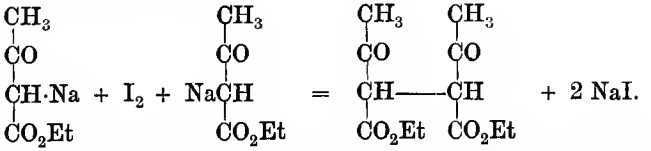
The pyrrol group of compounds has assumed of recent years a greatly increased importance from many points of view. It has been found, for example, that they, and especially the reduced pyrrol derivatives, are very widely distributed in nature. The pyrrol ring has been found by Pinner in nicotine, by Liebermann in hygrine, and by Willstätter in atropine and cocaine. Even more important natural substances have been shown to belong to this group. Thus the researches of Küster and others have proved that both haemoglobin and chlorophyll are to be regarded as derivatives of methyl-propyl pyrrol, and, as we have seen, Emil Fischer has proved that α-pyrrolidine carboxylic acid is a constituent of nearly all proteid substances.

If we add to this the great practical and theoretical importance of indigo and its allies, it is evident that the pyrrol group is one which deserves careful consideration.

The formula

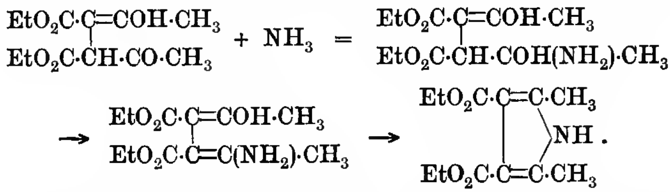


was proposed for pyrrol by Baeyer in 1870, and has maintained its position (with some reservation in respect to the distribution of the double bonds) up to the present day. It is supported by the relation between pyrrol and thiophene and furfurane, as well as by a whole series of syntheses in which derivatives of these three classes result from γ-dicarbonyl compounds, γ-diketones, γ-ketonic acids, &c. This method of synthesis was discovered by Knorr; perhaps the simplest example is the preparation of dimethyl-pyrrol from acetonyl-acetone, $CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CO \cdot CH_3$. The ketone itself is obtained by treating sodium acetoacetic ester with iodine, when two molecules condense to give diaceto-succinic ester :—



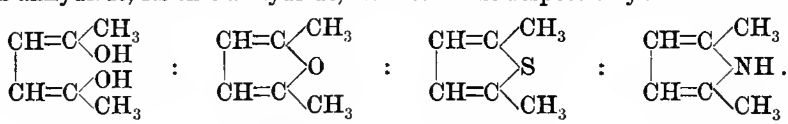
[1] See Ciamician, 'On the development of the chemistry of pyrrol in the last twenty-five years' [*Ber.* **37**. 4200 (1904)], a very full and clear account on which the following is largely based.

This diacetosuccinic ester (a body remarkable for the enormous number of tautomeric forms in which it can occur) is itself a γ-diketone, and therefore it will condense with ammonia to a pyrrol derivative, the ester of dimethyl-pyrrol dicarboxylic acid. Knorr and Rabe[1] have investigated this reaction in detail, and find that an intermediate compound is formed. It is probable that the ammonia first forms an addition-compound with the ester, and that this then loses first one molecule of water, and then a second, to give the pyrrol:—



The second of these bodies can actually be obtained by working in ethereal solution at 0°; at the ordinary temperature the third, the pyrrol, is produced. The same intermediate stages probably occur in all syntheses of this kind.[2]

In the ordinary Knorr synthesis of dimethyl-pyrrol the diacetosuccinic ester is left to stand with cold soda solution, which saponifies it and at the same time splits off the very unstable β-carboxyls, leaving acetonyl-acetone. The interest of this body lies in the fact that it is capable of giving all the three heterocyclic 5-rings. With a dehydrating agent it gives dimethyl-furfurane; with phosphorus pentasulphide, dimethyl-thiophene; and finally, with ammonia, dimethyl-pyrrol. If we disregard the intermediate compounds already referred to, these reactions are best written with the ketone in the dienolic form, when the products appear as its anhydride, its thio-anhydride, and its imine respectively:—

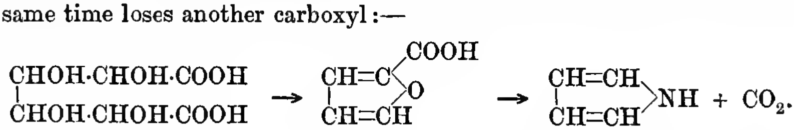


Acetonyl-acetone. : Dimethyl-furfurane. : Dimethyl-thiophene. : Dimethyl-pyrrol.

The methyl groups in dimethyl-pyrrol can then be oxidized to carboxyl and so eliminated, giving pyrrol: a fairly conclusive proof of its formula.

Knorr's synthesis is capable of great extension. Practically any γ-ketone, γ-ketonic acid, or γ-diketonic acid can be used, while the ammonia can be replaced by amines, hydrazines, or hydroxylamine. It is therefore of the utmost value for the production of compounds of this type.

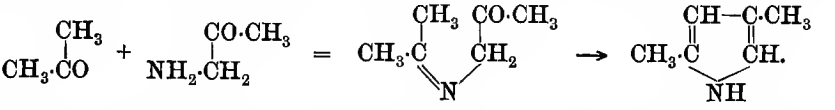
Pyrrol can also be got by distilling ammonium mucate or saccharate, or by heating them to 200° with glycerine. The mucic acid first forms pyromucic acid (furfurane α-carboxylic acid), which then reacts with the ammonia, and at the same time loses another carboxyl:—



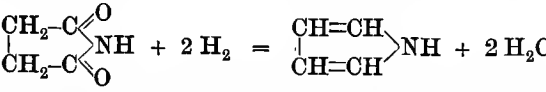
[1] *Ber.* **33**. 3801 (1900).

[2] Cf. Borsche, Fels, *Ber.* **39**. 3877 (1906).

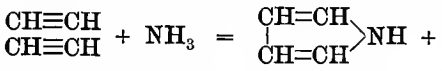
Another general reaction, also discovered by Knorr,[1] for the preparation of pyrrol derivatives, is that of ketones with amino-ketones, including ketonic acids. The method is to start with the easily obtained isonitroso-ketone, and reduce this to amino-ketone in the presence of the other ketone. This reaction, like the former, has been shown to go in two stages, an open-chain compound being first formed; for example, in the simplest case of acetone and isonitroso-acetone :—



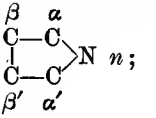
Pyrrol can also be formed (though only in traces) by the reduction of succinimide with zinc dust or sodium, which is an important proof of its formula :—



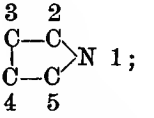
and by passing acetylene and ammonia through a red-hot tube :—



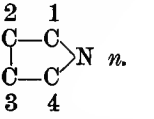
The positions of the substituents on the ring are indicated in three ways, which tends to confusion. The commonest and simplest way is



but Beilstein uses



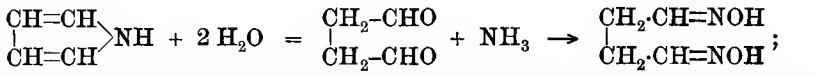
and there is a third method sometimes employed,



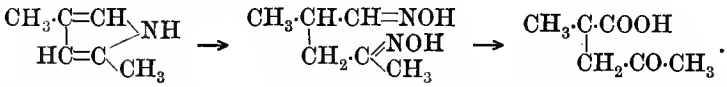
The formula of pyrrol is sufficiently proved by these syntheses, and is supported by the fact that the required number of isomers (e.g. three (*n*, *α*, *β*) mono-derivatives) are found to occur among the substitution-products. The position of the substituents is often known already from the synthesis; but an important method of determining it is by breaking the ring to form an open-chain compound. There are various ways in which the ring can be broken, and they are all really reversals of different syntheses. The method which is of most importance for our present purpose—that of orientation—is an indirect hydrolysis. Unlike the furfurane bodies, the pyrrols cannot be hydrolysed directly,

[1] *Ber.* **17.** 1635 (1884); *Ann.* **236.** 290 (1886).

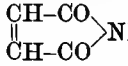
except in the case of a few complicated derivatives, the reason apparently being that the reverse action, that of closing the ring, occurs much more easily. But the hydrolysis is possible if a substance is present which can prevent this reversal of the action by combining with the product of hydrolysis. Such a substance is hydroxylamine. If a pyrrol is treated with an alkaline solution of hydroxylamine, it is at first hydrolysed to a dialdehyde, and this at once forms its dioxime :—

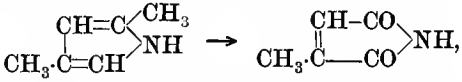


the body obtained from pyrrol itself being the dioxime of succinic aldehyde. This reaction enables us to determine the position of any number of substituents. If the substituent is on the nitrogen it is, of course, removed, giving the simple dioxime which, on hydrolysis with concentrated potash, is converted into succinic acid. If the alkyl groups are in the β- or β'-positions, they give by a similar reaction an alkyl succinic acid. If one α-hydrogen is substituted, the product is the dioxime not of a dialdehyde, but of a ketone-aldehyde, and on treatment with potash it is oxidized to a keto-acid. Thus α-β'-dimethyl-pyrrol gives β-aceto-isobutyric acid :—

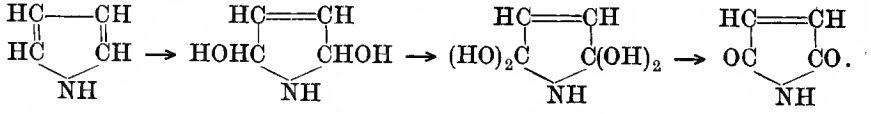


If both the α- and α'- are occupied, a diketone-dioxime is formed, which on hydrolysis gives only the diketone itself.

Another method of breaking the ring, which is also the reversal of a synthesis, is by oxidation. As pyrrol can be got by reducing succinimide, so it has been found[1] that pyrrol can be oxidized by chromic acid, not to succinimide, but to the previously unknown maleinimide,  ; and in the same way α-β'-dimethyl-pyrrol gives the imide of citraconic acid :—



the α-methyl being oxidized to carboxyl and eliminated. It is to be noticed that these oxidations are in strict accordance with Thiele's rule ; we are dealing with a conjugated system, and so the points of attack for the oxygen are the 1,4-positions, that is, the two α-carbon atoms. We may suppose that as usual the oxidizing agent adds on two hydroxyls at these points, while the double bond migrates to the 2,3-position ; and the hydrogen attached to the α-carbons is also oxidized to hydroxyl. We thus get :—

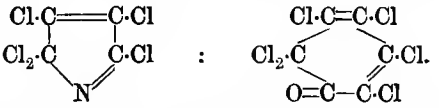


[1] Plancher, Cattadori, *Gazz.* **33**. i. 402 (1903).

Pyrrol itself is so called from πυρρός, fiery red, because it gives this colour to a pine shaving. It was discovered by Runge in 1834, in coal tar, and in 1858 by Anderson in bone oil, from which it is now practically always obtained. The bone oil is freed from its strongly basic constituents, mainly the pyridine compounds (pyrrol and its homologues are very weak bases), and then contains the nitriles of the fatty acids, the benzene hydrocarbons, and pyrrol and its homologues. The nitriles are removed by saponification with potash, and the liquid fractionated. The pyrrol is contained in the fraction boiling at 115–130°, and is isolated by conversion into the solid potassium pyrrol.

Pyrrol is a colourless liquid boiling at 131°, which smells like chloroform. It appears from its formula as a secondary amine, but its basic properties are extraordinarily weak. They are to some extent concealed by the fact that pyrrol and most of its homologues are very easily converted by strong acids into complicated polymers; but even where these bodies are not formed, and the salts can be obtained, they are at once hydrolysed by water. In dilute acids pyrrol only dissolves slowly; and the tendency of the nitrogen to pass into the pentad condition is so slight that it will not combine with alkyl iodide.

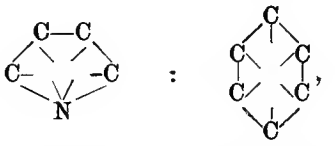
The weak basicity of the pyrrols is obviously related to their peculiar aromatic character. The remarkable point about this is that whereas thiophene and its homologues resemble the aromatic hydrocarbons, as has often been emphasized, the striking analogy of pyrrol is not to the hydrocarbons but to the phenols. Of this analogy many instances might be given. The imide hydrogen, like the hydroxyl hydrogen of the phenols, can be replaced by potassium, forming potassium pyrrol, C_4H_4NK. The hydrogen of the CH group, as in phenol, is extraordinarily easily replaced: for example, by the halogens. Indeed, the resemblance in the action of the halogens goes deeper than this. Tetrachloropyrrol, C_4Cl_4NH, can be further chlorinated to pentachloropyrrol, a derivative of a pseudo-form, analogous to the pseudophenol compounds, such as hexachlorophenol :—



The analogy is also shown in the formation of nitroso- and nitro-compounds; in the power of direct coupling with diazonium salts to give azo- and dis-azo-dyes; and in their behaviour on alkylation.

It would seem as if we ought to be able to give some reason for so striking a resemblance; but we can do no more than guess. We may take Baeyer's formula for pyrrol, $\begin{matrix}CH{=}CH\\ |\\ CH{=}CH\end{matrix}\!\!>\!NH$, as established; and the only question is as to the exact interpretation which is to be given, in the light of Thiele's discoveries, to the double bonds. The analogy to benzene is indicated by the undoubted aromatic character, though of a peculiar kind; and still more by the fact that on reduction this entirely disappears, the dihydro-pyrrols being much more unsaturated than pyrrol itself. From this point of view Bamberger, in 1891, before the publication of Thiele's theory, suggested that the so-called hexacentric

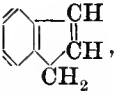
equilibrium was maintained in pyrrol by means of the two extra valencies of the nitrogen :—



and that this would explain the feeble basicity of pyrrol, since its nitrogen atom was pentavalent. But as regards the last argument, on which Bamberger chiefly insists, Marckwald[1] has pointed out that the fact that the NH is attached to two –C=C– groups is itself sufficient to explain its feeble basicity, as is illustrated by the cases of diphenylamine and dihydro-acridine,

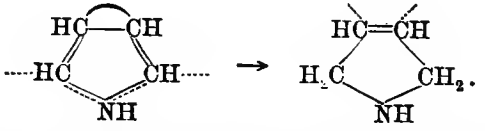


which contain the same grouping, and exhibit the same suppression of basic properties. The highly negative influence of this structure is further shown in indene,



the carbon-analogue of indol, where the two –C=C– groups communicate to the methylene a distinctly acidic character.

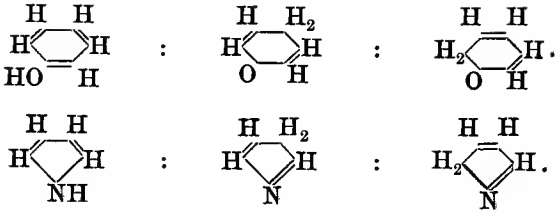
Thiele has now introduced a greater flexibility into our conception of linkages, and we may fairly adopt a modified form of Bamberger's suggestion. It must be modified, because pyrrol is much less completely saturated than benzene, as is shown by its behaviour on oxidation. But we may suppose that in pyrrol, and similarly in thiophene and furfurane, the higher valency of the nitrogen (or the sulphur or the oxygen) is partially exerted, and that thus there are two bonds which can go some way towards saturating the residual valencies of the carbons in the two α-positions. This would be expressed in Thiele's symbols by the formula



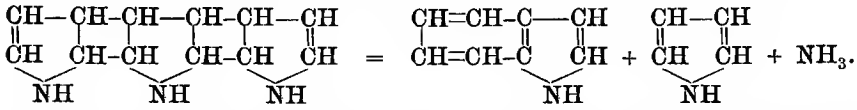
On reduction this passes as benzene does into an ordinary unsaturated system.

In this way we get an explanation of the peculiar, so to speak, semi-aromatic character of pyrrol.[2] As regards its striking resemblance to phenol, we can see some sort of reason for this also. The peculiarities of phenol are certainly due to a great extent to its power of assuming a second tautomeric form, from which the pseudophenols are derived: and pyrrol possesses the same power, the three forms corresponding exactly in the two cases :—

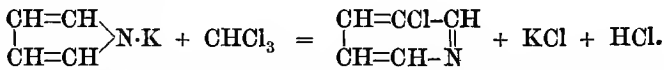
[1] *Ann.* **279**. 8 (1894); *Ber.* **28**. 114, 1501 (1895).
[2] Cf. Ciamician, *Gazz.* **35**. ii. 384 (*C.* **05**. ii. 1797).



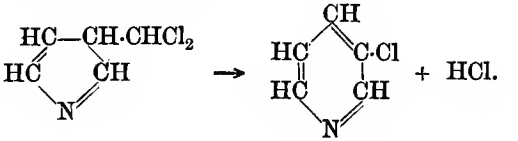
Pyrrol is characterized by a strong tendency to polymerization, shown, as it so often is, by a readiness to turn into a resin, which is no doubt a high polymer. All strong acids resinify it rapidly. If its ethereal solution is treated with hydrochloric acid, the salt of tripyrrol, $(C_4H_5N)_3 \cdot HCl$, is precipitated; and free tripyrrol may be obtained by neutralizing a solution of pyrrol in dilute hydrochloric acid with ammonia. It decomposes on heating into ammonia, pyrrol, and indol, whence its formula probably is:—



A very remarkable characteristic of the pyrrol ring is the ease with which it goes into the pyridine ring—one of the small class of cases of the expansion of rings which are to be noticed from their bearing on the question of the stability of ring structures. If potassium pyrrol is heated with chloroform it is converted into β-chloro-pyridine:—



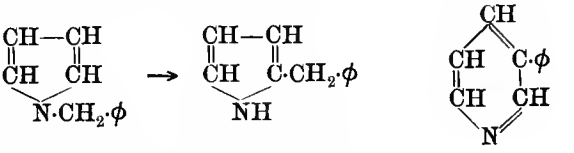
Many other halogen derivatives act in the same way, the methane carbon always going between the α- and the β-carbon atoms of the pyrrol, i.e. taking up the meta position to the nitrogen, and becoming the β-carbon atom of the pyridine.[1] Thus with bromoform, potassium pyrrol gives β-bromo-pyridine, with methylene iodide, pyridine itself, and with benzal chloride, β-phenyl-pyridine, and so forth. The reaction takes place with many of the homologues of pyrrol and with the indols more readily than with pyrrol itself. From experiments made with the indols and carbazols it is probable that the reaction goes in two stages. A pseudo-pyrrol derivative is first formed, and then the ring opens and admits the new carbon atom:—



The conversion of the pyrrol into the pyridine ring can also take place in other ways. If a derivative of pyrrol with the side chain either on the nitrogen or on

[1] Emerson Reynolds (*J. C. S.* **1909**. 505, 508) has tried to obtain compounds with silicon in the ring, by the action of silicon tetrachloride or silico-chloroform on potassium pyrrol, but without success.

the next (α-) carbon is passed through a tube at a low red heat, the carbon of the side chain enters the ring. Thus N-benzyl-pyrrol is converted first into α-benzyl-pyrrol, and then into β-phenyl-pyridine:—

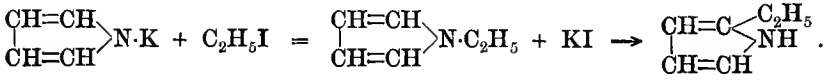


In the same way α-methyl-pyrrol gives pyridine.[1]

Derivatives of Pyrrol

Potassium pyrrol, $C_4H_4N{\cdot}K$, is formed with evolution of hydrogen by dissolving potassium in pyrrol: and also by boiling pyrrol with solid potash, which is a proof of the acidic character of the imine hydrogen. Sodium goes in much less readily. Soda has no action on pyrrol at all; and metallic sodium only turns out the hydrogen at a very high temperature. This may be compared with the much slower reaction of benzene, which acts on potassium at a high temperature to give potassium benzene, $C_6H_5{\cdot}K$, but does not act on sodium at all.

Potassium pyrrol is a solid crystalline substance, decomposed by water into potash and pyrrol. It is the source of a large number of pyrrol derivatives, as on treatment with alkyl and acyl halides, chlorocarbonic ester, &c., it gives the corresponding N-substituted pyrrols. These products are remarkable for the ease with which on heating the substituent passes from the nitrogen to the carbon, as so often happens in the case of aniline. For example:—

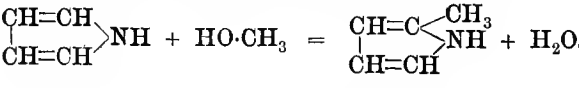


It appears that in these cases the α- and β-positions are occupied indifferently, a mixture of the two C-derivatives being generally obtained.

The further behaviour of the pyrrols on alkylation is extraordinarily complicated, and has not yet been fully made out. By a succession of reactions a series of pseudo-pyrrol, pyrroline, and pyrrolidine derivatives are produced, the alkyl groups being added on to the ring one after another.

The alkyl pyrrols are of two kinds, the N- and the C-compounds. The first class are obtained from potassium pyrrol, or by any of the syntheses, if an amine is substituted for ammonia. They closely resemble pyrrol itself.

The C-alkyl derivatives may be got from the N- by heating, or they may be formed by passing the mixed vapours of pyrrol and an alcohol over heated zinc dust. This is essentially a dehydrating action:—

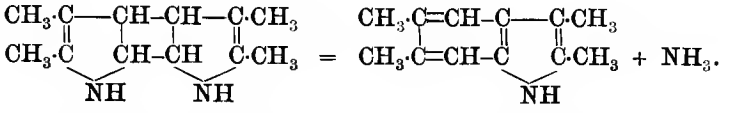


[1] Pictet, *Ber.* **38.** 1951 (1905).

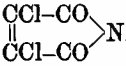
On further heating they are converted into pyridine derivatives. They can also be prepared by modifications of the various pyrrol syntheses; thus we have seen that acetonyl-acetone gives α,α'-dimethyl pyrrol.

They also resemble pyrrol, but both the imine and the methine hydrogens are often even more reactive. They are easily resinified by acids. Fusion with potash oxidizes the alkyls to carboxyls, giving rise to the pyrrol carboxylic acids.

The α-mono-alkyl and α,β-dialkyl compounds—i.e. those which have substituents only on one side of the molecule—when treated with hydrochloric acid in ethereal solution give double (not, like pyrrol itself, triple) polymers; and these when warmed with dilute sulphuric acid break up into ammonia and alkyl indols:—



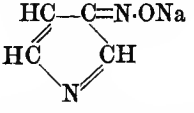
The halogens act on pyrrol with extreme violence, even more so than on phenol and aniline. The halogen must be very dilute, or the pyrrol resinifies; and even when it is dilute, it is not easy to stop short of a complete replacement of all the four hydrogen atoms attached to carbon.

Tetraiodopyrrol, obtained from tetrachloropyrrol and potassium iodide, is known as iodol, and is sometimes used as an antiseptic, having the same action as iodoform, but being free from the smell which generally accompanies the latter. An alkaline solution of chlorine or bromine both substitutes and oxidizes pyrrol, giving the imide of di-chloro-maleic acid,  .

The production by further chlorination of pseudo-pyrrol derivatives analogous to the pseudo-phenols, such as pentachloro-pyrrol, C_4Cl_5N, has already been mentioned.

The lower halogen derivatives have recently been prepared by the action of sulphuryl chloride in ethereal solution.[1] It is found that the halogen first occupies the α-positions and then the β-, and it is only when these places are filled up that the imine hydrogen is attacked. The conversion of these products by oxidation into substituted maleinimides gives a means of determining the position which the halogen has taken up.

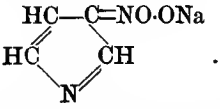
The nitrosopyrrols can be prepared by the action of amyl nitrite and sodium ethylate. This gives the sodium salt, which is really derived from the isonitroso-compound or oxime, e.g.



In the case of pyrrol itself only this sodium salt is stable, but in some of the derivatives the free compound can also be prepared.

[1] Mazzara, Borgo, *Gazz.* **35**. i. 477; ii. 100 (*C.* **05**. ii. 488, 829).

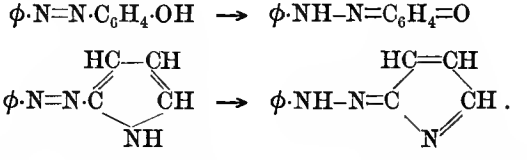
The nitropyrrols can be made by direct nitration in the case of the more stable compounds, such as the carboxylic acids. Otherwise it is necessary to use amyl nitrate and sodium ethylate, which give the sodium salt of the isonitro-compound :—



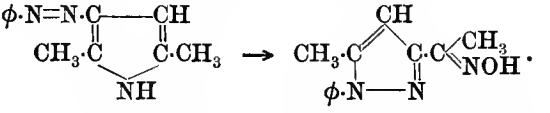
This is a very unstable compound, which explodes like gunpowder when touched with a hot wire. The dinitropyrrols are stable, though their salts also are explosive.

The aminopyrrols[1] can be prepared from the nitroso- or the nitro-derivatives by reduction with zinc and acetic acid. They resemble the aromatic amines in being converted into diazo-compounds by nitrous acid. They are somewhat unstable bodies, as are the aminophenols.

The azopyrrols are formed, like the azophenols or oxy-azo-compounds, by the direct coupling of the pyrrols with diazonium salts. The diazo-group takes up the α-position, and only goes to the β- when the α- is occupied. The products closely resemble the oxy-azo-bodies, and like them are dyes. They also show the same tendency as the oxy-azo-bodies to go over into a tautomeric hydrazone form :—



The β-azo-derivatives, obtained from compounds in which the two α-positions are already occupied, undergo a remarkable change when heated with excess of hydroxylamine, being converted into pyrazoles[2] :—



This implies that the ring first opens, and then closes again through the azo-group.

The pyrrol carboxylic acids can be made by introducing carboxyl into pyrrol by any of the methods used in the case of phenol: for example, by heating potassium pyrrol in a stream of carbon dioxide, or by acting on pyrrol with chloroform in the presence of alcoholic potash (Tiemann and Reimer's reaction). In either case an α-acid is obtained. The alkyl-pyrrols cannot be oxidized to acids by potassium permanganate, as in the benzene series, but only by fusion with potash; in this they resemble the phenols. But if the ring contains an acyl group, as $CH_3 \cdot CO$, as well as an alkyl, then the alkyl can be oxidized to

[1] Angelico, *C.* **05**. ii. 900; Angeli, Marchetti, *C.* **08**. i. 739.
[2] Castellana, *Gazz.* **36**. ii. 48 (*C.* **06**. ii. 1126).

carboxyl by permanganate, though in this case the acyl only yields to potash fusion.

The carboxylic acids of pyrrol resemble those of phenol in many respects. They lose carbon dioxide even more easily than the latter, often merely by boiling with water, or by heating alone above their melting-points. This, however, is a common property of carboxyl attached to a nitrogenous ring.

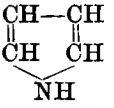
It is remarkable that the β-acids, both of pyrrol and of indol, are much weaker than the corresponding α-acids, as is shown by the following values of the dissociation constant K[1]:—

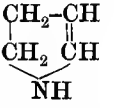
α-pyrrol-carboxylic acid	0·00403
β- ,, ,, ,, ...	0·00012
α,β-dimethyl-pyrrol α′-carb. acid . . .	0·0002 (about)
α,β- ,, ,, β′- ,, ,, . . .	0·000075
α-indol-carboxylic acid	0·0177
β- ,, ,, ,, ...	0·00056

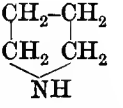
This is the more strange since the opposite is the case with the acids of pyridine:—

α- 0·0003 : β- 0·00137 : γ- 0·00109.

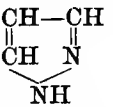
The reduced pyrrol derivatives are of less importance. Their nomenclature should be observed, as it is typical of that adopted in all these heterocyclic compounds. By treating pyrrol with zinc and acetic acid, two hydrogen atoms are introduced, and dihydropyrrol is formed, which on treatment with hydriodic acid and phosphorus takes up two more hydrogen atoms to give tetrahydropyrrol. Dihydropyrrol is known as pyrroline, tetrahydro- as pyrrolidine: one syllable being added for every pair of hydrogen atoms:—

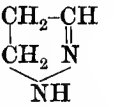

Pyrrol.

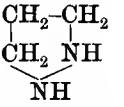

Pyrroline.


Pyrrolidine.

This system is always used: thus we have in the pyrazole series:—


Pyrazole.


Pyrazoline.

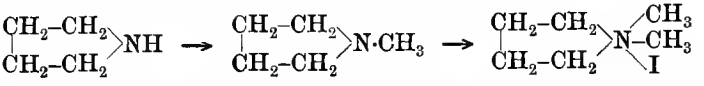

Pyrazolidine.

The reduced pyrrols have entirely lost the peculiar aromatic character of pyrrol, and behave as unsaturated or saturated fatty compounds. Thus pyrroline is a strong base, forming stable salts with acids, and giving a quaternary iodide with methyl iodide. The further reduction of the pyrrolines to pyrrolidines is not easy. It requires the action of hydriodic acid and phosphorus, and it is difficult to prevent this from going too far, and giving an alkylamine or even a hydrocarbon.

Pyrrolidine is tetramethylene imine, and can be made, as has already been

[1] Angeli, *Gazz.* **22**. ii. 1 (1892).

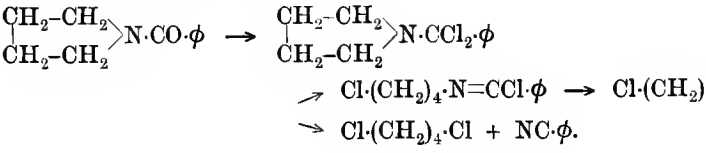
mentioned, by heating the hydrochloride of tetramethylene diamine. In its physical and chemical properties it closely resembles the next member of the series, pentamethylene imine or piperidine. When rapidly heated or distilled over zinc dust it is converted into pyrrol. It shows the characteristic behaviour discovered by Hofmann for piperidine on what is known as exhaustive methylation. This is the effect of continued treatment with methyl iodide, and is a remarkable series of reactions, which has often proved of great value in elucidating the structure of the nitrogenous rings of the alkaloids. In the case of pyrrolidine the successive stages are as follows :—



$$\rightarrow CH_2{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}N(CH_3)_3I \rightarrow CH_2{=}CH{\cdot}CH{=}CH_2 + N(CH_3)_4I.$$

The main effect of these reactions is to split off the nitrogen from the ring first on one side and then on the other, in each case with the production of an ethylene group, the final product being trimethylamine and a doubly unsaturated hydrocarbon. In the same way β-methyl-pyrrolidine can be converted into isoprene, $CH_2{=}C(CH_3){\cdot}CH{=}CH_2$.

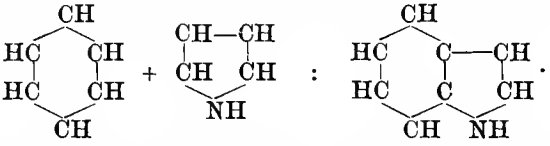
A somewhat similar reaction is that of phosphorus pentachloride on benzoyl-pyrrolidine (and also on benzoyl-piperidine).[1] According to the conditions the ring can be split off on both sides from the nitrogen, or only on one, its place being taken by chlorine :—



[1] v. Braun, Beschke, *Ber.* **39.** 4119 (1906).

INDOL GROUP

If a benzene nucleus is imagined to condense with a pyrrol nucleus so that the resulting compound has two ortho-carbon atoms of the benzene identical with the α- and β- of the pyrrol, we get a body bearing the same relation to pyrrol that naphthalene does to benzene, whose systematic name is benzopyrrol :—

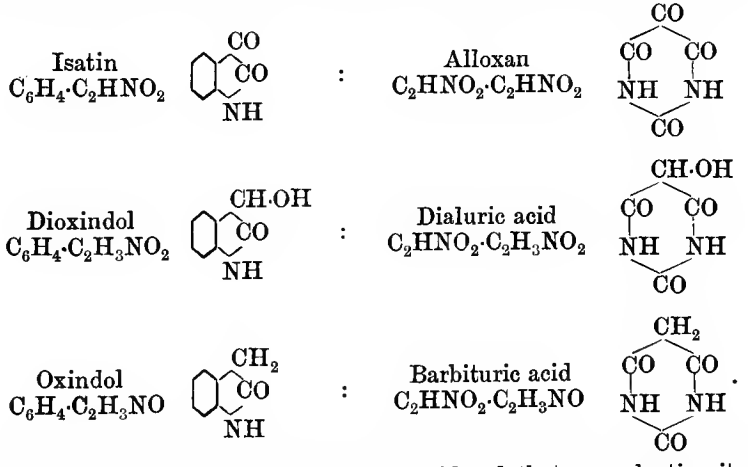


This body is indol, the mother substance of indigo and its derivatives. This group of compounds is for various reasons of the highest importance. The physical and chemical properties of indigo early attracted the attention of chemists. Its volatility and its bronzy lustre seemed particularly mysterious, and the latter was at one time supposed to indicate something of a metallic

nature. In a more scientific age, the desire to elucidate the constitution of the substance was naturally stimulated by the hope of discovering a method of preparing artificially the most valuable and most beautiful of natural dyes. The history of the steps by which these two problems, so closely interwoven—the scientific and the technical—were ultimately solved by the labours of Baeyer and others, extending over the last forty years of the nineteenth century, forms one of the most interesting chapters in the history of chemistry.[1]

The main credit of these great achievements belongs of course to Baeyer, who seems to have been destined by nature from a very early age for the investigation of the subject. But the scientific examination of indigo began many years before his time, and in the first half of the nineteenth century several valuable benzene derivatives were obtained from it. Thus in 1826 Unverdorben prepared aniline from it by dry distillation; and in 1841 Fritsche obtained by oxidation anthranilic acid (*o*-amino-benzoic acid), a body which has since become important in connexion with the synthesis of indigo.

The first work which was really of value for the elucidation of the formula was Laurent and Erdmann's discovery that indigo when oxidized with nitric acid yields isatin, $C_8H_5NO_2$. They were not able to throw much light on the structure of this body, though it was clearly a benzene derivative; and for some years the subject was not further investigated. Then Baeyer took it up, and showed that isatin, $C_6H_4{\cdot}C_2HNO_2$, could be converted by reduction first into dioxindol, $C_6H_4{\cdot}C_2H_3NO_2$, and then into oxindol, $C_6H_4{\cdot}C_2H_3NO$. Baeyer had just been working on barbituric acid and its derivatives, and had proved barbituric acid to be malonyl-urea: and he was struck by the remarkable resemblance of the series isatin, dioxindol, oxindol, to the series alloxan, dialuric acid, barbituric acid, a resemblance fully borne out by their modern formulae :—



He regarded oxindol as a phenol, and considered that on reduction it should give a body in which the hydroxyl was replaced by hydrogen, which he called

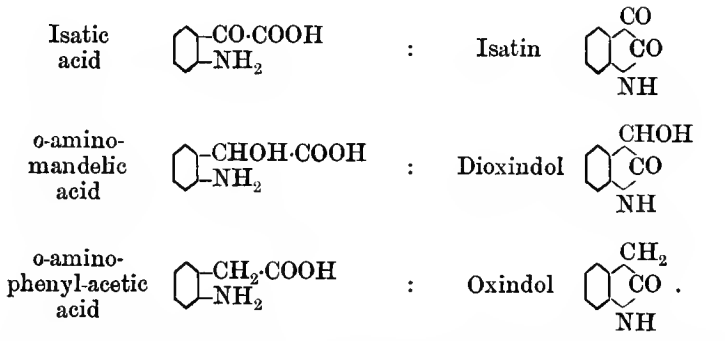
[1] This subject was summarized from the scientific side by Baeyer, and from the technical side by Brunck, in two lectures delivered at the opening of the Hofmannhaus in Berlin in 1900 (*Ber.* **33**. *Sonderheft*, li, lxxi). The following account is largely based on these papers.

indol. This he actually prepared in 1866 by passing oxindol vapour over heated zinc dust—a method introduced here for the first time, and adopted immediately afterwards by Graebe and Liebermann for the conversion of alizarine into anthracene, by which they were led to the synthesis of alizarine.

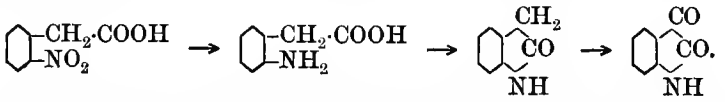
In 1869 Kekulé suggested that isatic acid, which is formed from isatin by the addition of a molecule of water, and readily passes back into isatin again, was amino-benzoyl-formic acid, and isatin its anhydride:—

Isatic acid $C_6H_4\langle^{CO\cdot COOH}_{NH_2}$: Isatin $C_6H_4\langle^{CO\cdot CO}_{NH}$.

He suggested that it might be synthesized from o-nitro-phenyl-acetic acid, but he was unable to prepare this acid, and so could not test the synthesis. Baeyer saw that if Kekulé's view was right, the reduction-products of isatin, dioxindol and oxindol, might be similarly formed anhydrides of the reduction-products of o-amino-benzoyl-formic acid, i. e. of o-amino-mandelic acid and of o-amino-phenyl-acetic acid:—



He proved that isatic acid gave on reduction o-amino-mandelic acid, which on further reduction gave oxindol: and on June 6, 1878, he for the first time synthesized isatin from o-nitro-phenyl-acetic acid by reduction to oxindol, followed by oxidation:—



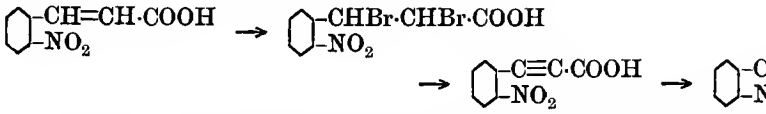
As he had already, in 1870, prepared indigo from isatin by treatment with phosphorus pentachloride and reduction, this was the first true synthesis of indigo.

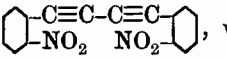
The formulae of isatin, dioxindol, oxindol, and indol were thus determined by the year 1878. The question of the formula of indigo still remained. It was certainly closely related to the indol derivatives, as was shown by its formation from isatin. Its synoptic formula was proved by analysis and vapour density to be $C_{16}H_{10}N_2O_2$, while that of isatin is $C_8H_5NO_2$. Hence indigo is formed by the condensation of two molecules of isatin with the loss of two atoms of oxygen. It was therefore to be expected that it would be obtained by the reduction of isatin. But Baeyer had shown that isatin could be reduced by successive stages

through dioxindol and oxindol to indol itself, which contains no oxygen at all, without indigo being formed in the process. He had further shown that in dioxindol and oxindol it was the β-carbonyl which was reduced, and he therefore suggested that the presence of the carbonyl group in the β-position may be necessary to the formation of indigo.

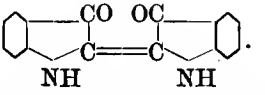
We are practically sure, then, from the relation of indigo to the indol group, that it contains the same nucleus as indol,  . We know that it consists of two such nuclei joined together, no doubt by means of the pyrrol ring. The next question is how this junction is effected, whether through the carbon or the nitrogen. If it is through the carbon, it is probably the α- and not the β-, since the presence of a β-carbonyl seems to be required for the production of indigo.

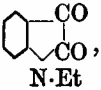
This question was settled by Baeyer in 1882, by the synthesis of indigo from di-*o*-dinitro-diphenyl-diacetylene. *o*-nitro-cinnamic acid forms a dibromide which when treated with alkali loses two molecules of hydrobromic acid, and gives *o*-nitro·phenyl-propiolic acid :—



This acid loses carbon dioxide to form *o*-nitro-phenyl-acetylene, and when the copper derivative of this is oxidized with potassium ferricyanide, two molecules condense to give di-*o*-dinitro-diphenyl-diacetylene,  , which on reduction yields indigo.

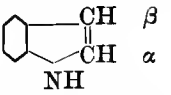
This proves that the two phenyl nuclei in indigo are joined by an unbranched chain of carbon atoms: or, in other words, that the two indol nuclei are joined together through the two α-carbon atoms ; and this gives, as the most probable formula for indigo,



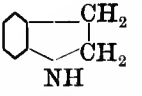
The only other possible formula would have the hydrogen attached to the oxygen instead of the nitrogen. This, however, was shown by Baeyer to be impossible, for the following reason. The N-ethyl ether of isatin,  , condenses like isatin itself to diethyl-indigo, which must therefore have two ethyl-imino-groups, and this substance exactly resembles indigo in its properties. It follows that indigo must contain two imine groups, and so have the formula which Baeyer assigned to it.

This is in outline the history of the discovery of the constitution of indigo and the indol compounds. Before considering the individual substances in detail, it will be well to give a list of the more important of them.

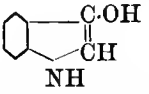
They are all derived from indol or benzopyrrol, and from dihydro-indol or benzopyrroline, a body which has been recently isolated: most of them from either, according as we regard them as enols or ketones. By replacing the α- or β-hydrogen, or both, in either of these bodies, by hydroxyl or ketonic oxygen, we arrive at the following compounds:—



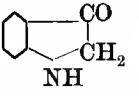
Indol, benzopyrrol.



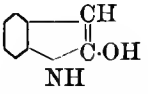
Dihydro-indol, indoline, benzopyrroline.



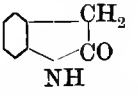
β-oxy-indol, indoxyl.



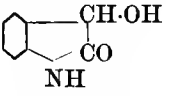
β-indolinone, pseudo-form of indoxyl.



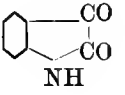
α-oxy-indol, oxindol, enol form.

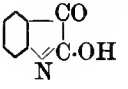


Oxindol, keto-form.

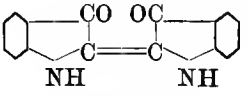


Dioxindol.



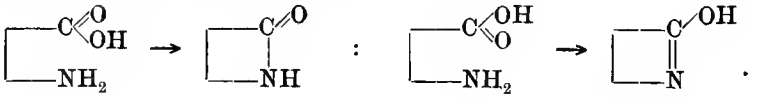


Isatin.

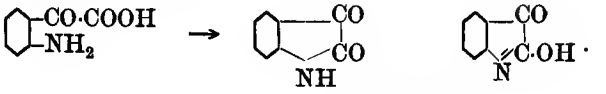


Indigo.

Of these compounds, those which have the α-carbon oxidized (oxindol, dioxindol, and isatin) are the lactames or lactimes of *o*-amino-benzoyl-formic acid and its reduction-products. These names are intended to indicate the analogy of the products to the lactones on the one hand and the amides or imides on the other. They are formed by loss of water between the NH_2 group (instead of the OH, as in the lactones) and the carboxyl: and this may occur in two ways. Either the OH of the carboxyl goes out with one hydrogen of the NH_2, giving a kind of amide, or the :O of the carboxyl with both hydrogens of the NH_2, giving an intramolecular imide:—



It is to be noticed that the two formulae are desmotropic, and are related in the same way as ketone and enol:—



Isatin.

Lactame. Lactime.

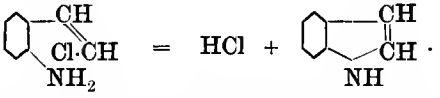
Compare:—



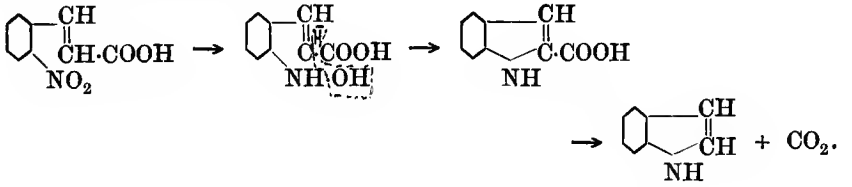
Ketone. Enol.

Indol or benzopyrrol is a crystalline solid, melting at 52° and boiling at 245°. It is obtained from its oxy-derivatives such as indigo and indoxyl by treatment with zinc dust (Baeyer, 1866–8) or sodium amalgam. A large number of syntheses have subsequently been discovered by Baeyer and others, of which the following are the most important.

1. From *o*-amino-ω-chloro-styrol by treatment with sodium ethylate (removal of hydrochloric acid):—

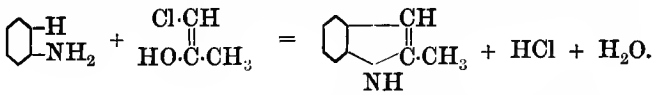


2. From o-nitro-cinnamic acid by reduction, the NO_2 being first converted into a hydroxylamine group:—



Indol is also formed to a small extent by passing the vapour of methyl-*o*-toluidine together with hydrogen over reduced nickel at 300°.[1] This reaction is reversible, and indol may in the same way be partially reduced to methyl-*o*-toluidine.

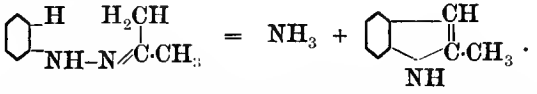
The alkyl-indols may be prepared in various ways. For example, from aniline and chloro-acetone, the latter reacting in the enolic form:—



Another way is from acetone and phenyl-hydrazine in presence of sulphuric acid or zinc chloride.[2] The hydrazone which is first formed eliminates an atom of nitrogen as ammonia from the middle of the chain in a peculiar manner, so

[1] Carrasco, Padoa, *C.* **06.** ii. 683; **07.** i. 571. [2] Plancher, Caravaggi, *C.* **05.** i. 1154.

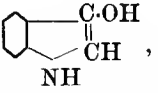
as to form the stable 5-ring; but the reaction proceeds quite smoothly and gives an excellent yield:—

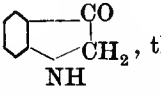
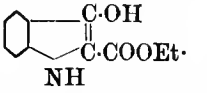


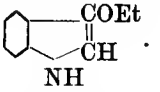
Indol itself resembles pyrrol in many respects. Its solution dyes a pine shaving moistened with alcohol and hydrochloric acid a cherry red. It is only feebly basic, and is easily resinified.

The homologues of indol resemble indol in properties, but are more stable towards acids. They all, except the α,β-dialkyl compounds, give the pine-shaving reaction. On fusion with potash the side chains are oxidized to carboxyl, giving the indol carboxylic acids.

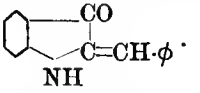
Dihydro-indol is made by reducing N-methyl-indol with zinc and hydrochloric acid to N-methyl-indoline, and heating this with hydriodic acid and phosphorus, whereby the methyl group is split off.[1] It is a liquid boiling at 220–221°.

Indoxyl, or β-oxy-indol,  , occurs in the indigo plant as the glucoside indican, and may be obtained by fusing indigo with potash in the absence of air. It is an unstable oil which is rapidly oxidized by the air to indigo. It is one of the intermediate products in the commercial manufacture of indigo.

Indoxyl is tautomeric. It can react also as a ketone,  , the form known as pseudo-indoxyl, which, however, is not capable of separate existence. In favour of the enol form there are many reactions. Indoxylic ester behaves as a phenol, dissolving in alkali, and being reprecipitated by carbon dioxide. It must therefore be  . It gives with ethyl iodide an ethyl ether, and this saponifies to ethyl-indoxylic acid (the phenol ether), which loses carbon dioxide to form ethyl indoxyl,

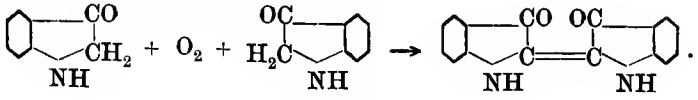


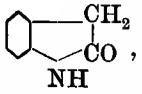
On the other hand, indoxyl and indoxylic acid react with aldehydes and ketones in the pseudo-form: thus with benzaldehyde they give:—

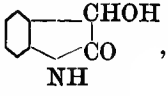


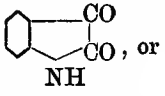
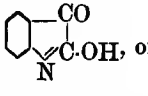
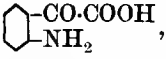
[1] Plancher, Ravenna, *C.* **05.** ii. 335.

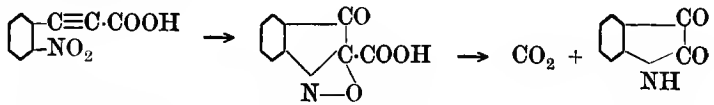
It is to be noticed that the oxidation of indoxyl to indigo is most simply represented as a reaction of the keto-form :—



Oxindol, or α-indolinone,  , melts at 120°. It is the lactame of *o*-amino-phenyl-acetic acid, into the barium salt of which it is converted by heating with baryta to 150°. So great is the tendency to close the ring that the free acid is incapable of existence : if the barium salt is treated with acid the oxindol is formed at once. (Compare the behaviour of the γ-oxy-acids.) It is also produced by the reduction of dioxindol, and hence of isatin.

Dioxindol,  , is the lactame of *o*-amino-mandelic acid, which also can only exist in the form of its salts, and passes over as soon as it is set free into the lactame.

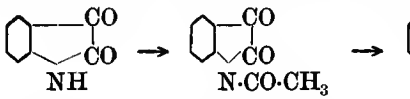
Isatin is the lactame,  , or lactime,  , of *o*-amino-benzoyl-formic acid,  , generally known as isatic acid, which can be isolated, but if warmed in aqueous solution goes over into isatin. Isatin forms orange red prisms, melting at 201°. It was first obtained by the oxidation of indigo, and was first synthesized by Baeyer from *o*-nitro-phenyl-acetic acid. Baeyer also synthesized it from o-nitro-phenyl-propiolic acid, which on treatment with alkali is transformed into the so-called isatogenic acid, which then loses carbon dioxide to give isatin :—



o-nitro-phenyl-propiolic acid. Isatogenic acid. Isatin.

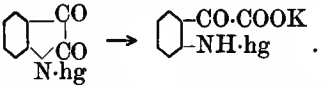
It is also formed by the oxidation of oxindol and of dioxindol. If it is reduced with zinc and hydrochloric acid it goes back into dioxindol.[1]

Isatin was one of the earliest observed cases of tautomerism. It forms an acetyl derivative, which must have the acetyl attached to nitrogen, since it yields acetyl-isatic acid. It is therefore derived from the lactame form :—

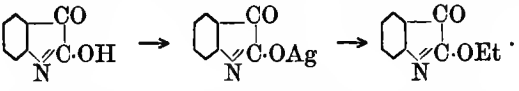


[1] Hydro-isatin, the supposed intermediate reduction-product of isatin, has been shown not to exist. Heller, *Ber.* **37**. 938 (1904).

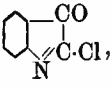
On the other hand, silver isatin gives with ethyl iodide an ether which must have the alkyl attached to oxygen, as it is readily saponified to isatin. This would not in itself prove that the silver in the salt is on the oxygen; but it is fairly good evidence of this [1] that the silver is removed as silver oxide when the salt is treated with potash. The mercury compound, on the other hand, must be an N-salt, for on treatment with potash the metal is not removed, though the ring is broken and a potassium salt of the mercury compound is formed:—

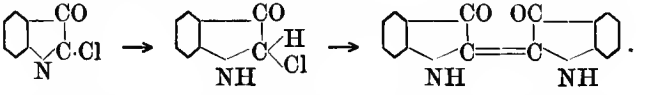


We may therefore assume that the silver salt is derived from the lactime form:—



Free isatin probably has the lactame structure, both in the solid state and in acid solution. Goldschmidt and Meissler [2] have shown that its reaction with phenyl isocyanate is in accordance with this view, and Hartley and Dobbie [3] have been led to the same conclusion by a study of the absorption spectrum. On the other hand, the alkaline solution and the alkaline salts appear to possess the tautomeric enol structure. The change from one to the other can be shown by means of a characteristic colour change.[4] Isatin dissolves in soda to form a bluish-red solution of the N-salt. On standing at the ordinary temperature the colour soon changes to pale yellow, owing to the formation of the O-salt. The salt of isatic acid is not formed unless the solution is boiled. If the yellow solution of the O-salt is acidified, the colour only gradually goes back to reddish, and then the isatin crystallizes out.

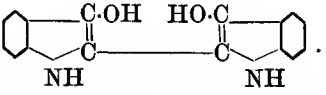
When treated with phosphorus pentachloride, isatin reacts, as we should expect, according to the enol formula (compare the case of uric acid), and gives isatin chloride,  , which on reduction with zinc and acetic acid, or with hydriodic acid, gives indigo. It is probable that the first effect of the reduction is to add on two atoms of hydrogen, with the formation of chloro-indoxyl, which then simply loses hydrochloric acid:—



Indigo, sometimes known as indigotin, occurs in the form of indican (probably a glucoside of indoxyl) in the indigo plant (*Indigofera Tinctoria*) of China and India, and in smaller quantities in the European woad (*Isatis Tinctoria*). To obtain it from the indigo plant, this is crushed in water and allowed to stand exposed to the air. An enzyme contained in the cells of the

[1] Peters, *Ber.* **40**. 235 (1907).
[2] *Ber.* **23**. 253 (1890).
[3] *J. C. S.* **1899**. 640.
[4] Cf. Heller, *Ber.* **37**. 938 Anm. (1904).

plant breaks up the indican into glucose and indoxyl, and the latter is oxidized by the air to indigo.[1] In dyeing with indigo two processes are employed. Either the dye is dissolved in sulphuric acid, and so converted into a disulphonic acid which is soluble in water and can be used for dyeing directly (Saxon process), or it is reduced to the leuco-base, indigo-white, by treatment with grape sugar in alkaline solution. The cloth is then dipped in this and the leuco-base oxidized on the fibre by the air. This indigo-white is probably a di-indoxyl:—



Indigo is a dark blue powder with a coppery-red reflection when rubbed. It is without smell or taste. It is insoluble in water, alkalies, acids, alcohol, and ether; but dissolves in aniline, molten paraffin, and some other organic substances, crystallizing out again on cooling. It has been found[2] that if indigo-white is oxidized in a solution containing certain colloidal substances, the indigo, instead of being precipitated, remains in solution in a soluble colloidal form. The best substances to employ as colloids are the higher hydrolytic products of the proteids, such as lysalbic acid. The solution is quite stable, and on evaporation leaves the indigo behind as a blue friable amorphous mass, easily soluble in water. It would seem, however, that this soluble form is a compound of indigo with lysalbic acid. From its aqueous solution the indigo is precipitated in the ordinary insoluble form by organic acids.

Indigo is further remarkable for its volatility. It forms a dark red vapour on heating, and under diminished pressure can be sublimed without decomposition.

The molecular weight of indigo in solution has been examined by Vaubel,[3] with rather unsatisfactory results. His work has been repeated by Beckmann and Gabel,[4] who find that indigo gives the normal molecular weight by the boiling-point method in all the solvents investigated (quinoline, aniline, phenol, and *p*-toluidine). The same value was obtained by the freezing-point method in aniline and phenol. But the lowering of the freezing-point of *p*-toluidine indicates a double molecular weight, so that it appears that in this solvent the molecules of indigo are double at the freezing-point (45°) but single at the boiling-point (198°). The crystals of *p*-toluidine which separate out are quite colourless, so that there can be no question of the results being vitiated by the formation of a solid solution.

The constitution of indigo has already been discussed. The main points are:—

1. Its relation to indoxyl and isatin shows it to contain two benzopyrrol nuclei.

2. Its formation from di-(*o*-nitro-phenyl-)-diacetylene shows that these two nuclei are joined through the two α-carbon atoms.

[1] Cf. Bergtheil, *J. C. S.* **1904**. 870.
[2] Möhlau, Zimmermann, *C.* **03**. i. 640.
[3] *C.* **01**. ii. 779; **02**. i. 936.
[4] *Ber.* **39**. 2611 (1906).

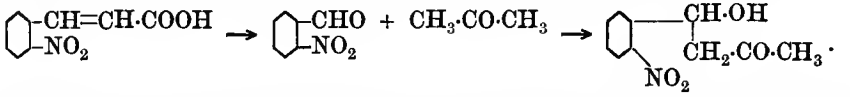
3. The production of N-diethyl-indigo with properties similar to those of indigo shows that it contains two NH groups.

The syntheses of indigo are very numerous, and some of them have been mentioned already. The more important are the following:—

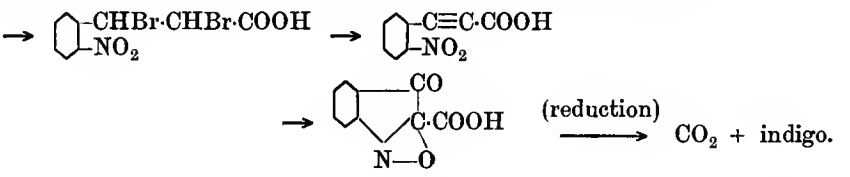
The first true synthesis was completed by Baeyer in 1878, when he synthesized isatin from *o*-nitro-phenyl-acetic acid, as he had shown in 1870 that isatin can be converted into indigo.

There are also a whole series of syntheses which Baeyer has worked out, starting with *o*-nitro-cinnamic acid.

The acid may be oxidized with permanganate to *o*-nitro-benzaldehyde: this condenses with acetone to the methyl ketone of *o*-nitro-phenyl-lactic acid, which, on treatment with alkali, gives acetic acid, water, and indigo:—



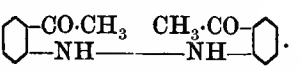
Or it may be converted by bromine into the dibromide, and this with alcoholic potash into the propiolic acid: which, on reduction in alkaline solution, gives first isatogenic acid, and then loses carbon dioxide to form indigo:—



Lastly, the propiolic acid may be converted by loss of carbon dioxide into *o*-nitro-phenyl-acetylene, and this condensed by the action of potassium ferricyanide to the diacetylene derivative, which, on treatment with alkali and reduction, yields indigo.

Since indigo can be obtained from indoxyl and from isatin, every new synthesis of either of these bodies is a synthesis of indigo. Indoxyl is converted into indigo by oxidation, while isatin (acting in the pseudo-form) is converted by phosphorus trichloride into isatin chloride, which is reduced by zinc dust through α-chloro-indoxyl to indigo.

A comparatively simple synthesis is that of Camps.[1] o-Nitro-acetophenone is converted by a variety of reducing agents (stannous chloride and hydrochloric acid, aluminium amalgam, zinc dust, &c.) into the corresponding hydrazo-compound, di-*o*-diaceto-hydrazobenzene:—



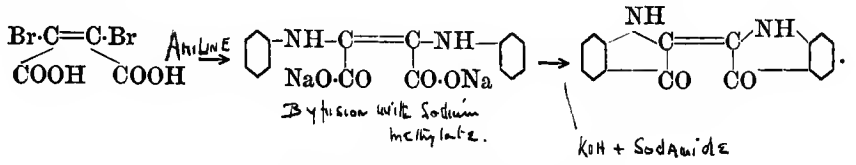
When this is heated alone it is converted largely into indigo, together with various reduced decomposition-products.

Another remarkable method[2] starts with dibromo-maleic acid. If this is heated with aniline it gives dianilido-maleic anhydride. Sodium methylate

[1] *C.* **02.** ii. 939.

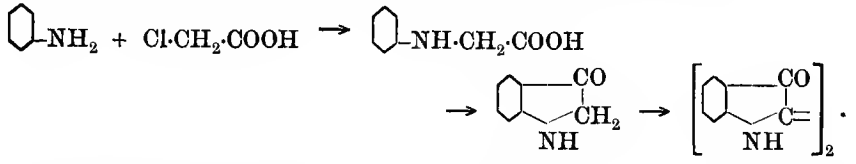
[2] Salmony, Simonis, *Ber.* **38.** 2580 (1905).

converts this into its sodium salt, which, when fused with potash and sodamide, gives indigo:—

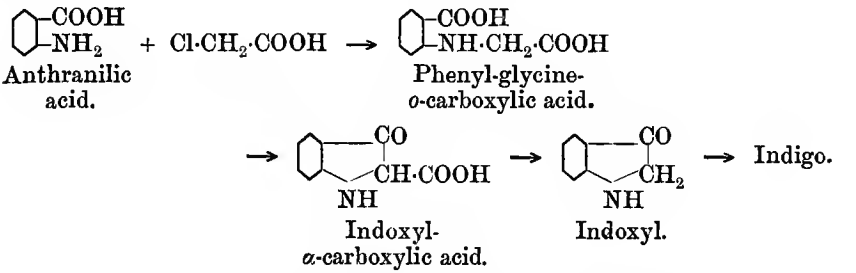


Commercial Synthesis of Indigo

The most important synthesis of indigo still remains to be described. It is that by which indigo is now prepared on the large scale, and is known as Heumann's synthesis. In its original form aniline was condensed with chloracetic acid to give phenyl-glycine. This, when treated with alkali or sulphuric acid, loses water and goes into indoxyl, which on oxidation yields indigo:—



An important improvement was the substitution of anthranilic acid (*o*-amino-benzoic acid) for aniline. This is converted by the same series of reactions through phenyl-glycine-*o*-carboxylic acid into indoxyl-carboxylic acid. This body loses carbon dioxide to form indoxyl, which is oxidized as before to indigo:—



The following account of synthetic indigo is mainly taken from Brunck's paper already referred to, and so represents the state of the industry in 1900.

The commercial preparation of synthetic indigo was, from the beginning of the aniline dye industry, an object of the researches of chemists. But the earlier syntheses of indigo were useless from a commercial point of view; and it was not till 1880, when Baeyer discovered the synthesis from *o*-nitro-phenyl-propiolic acid, that the question became one of practical importance. The first patent was taken out by Baeyer on the 19th of March, 1880. But it was only after this had been followed by nearly twenty years of continuous research that the present process, covered by 152 patents in Germany alone, was arrived at, and the synthetic product obtained at a price which could compete with that of the natural indigo.

By 1881 the synthesis from *o*-nitro-phenyl-propiolic acid was so far improved that indigo could be made at a cost not much greater than that of the natural product, and it was actually employed to a limited extent in cotton-printing.

In 1882 Baeyer's method of preparation from *o*-nitro-benzaldehyde appeared. This was an improvement on the older method, but only a slight one. Indeed, there was a fundamental objection to both of these methods which must, in spite of an improvement in detail, have prevented them from becoming serious rivals of the natural process. They both start with toluene, and the supply of toluene is necessarily very limited, and so must have limited the supply of artificial indigo. Toluene is of course obtained entirely from the distillation of coal tar, of which the main product is benzene. The annual production of benzene and toluene together amounts to 25,000–30,000 tons, which is almost wholly used for dyeing, and consists of only about one part of toluene to four of benzene. Thus only 5,000–6,000 tons are produced annually, which no more than suffice for the present demand. Any increase in this production must be accompanied by four times as great an increase in the production of benzene, and therefore by an enormous rise in the price of toluene, unless a demand could be created for this additional quantity of benzene.

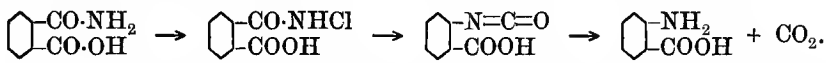
Now, by the most recent and improved methods, 1 kilogram of indigo cannot be obtained from less than 4 kilograms of toluene ; and the annual consumption of indigo amounted, before the introduction of the synthetic compound, to 5,000 tons. Thus the whole of the present production of toluene would only produce a quarter of the indigo consumed ; and in order to replace entirely the natural by the artificial indigo it would be necessary to produce five times as much toluene as is now prepared, and hence to increase the annual production of benzene by at least 80,000 tons, for which there is no demand.

It was therefore evidently necessary to find some other source for indigo ; and so the problem entered on a new stage when, in 1890, Heumann discovered the synthesis from phenyl-glycine. The raw materials required for this were aniline, acetic acid, chlorine, and alkali, which could all be obtained in any quantity. But the yield by this method was small and the cost great ; and it was not until Heumann discovered that the substitution of anthranilic acid for aniline gave a much better yield, that the method could be used on the large scale. Then, indeed, the problem was in outline solved. But it still required seven years of unremitting labour, taxing the utmost resources both scientific and technical, in inorganic as well as organic chemistry, of the two greatest dye factories in the world, before the details of the process could be sufficiently improved to admit of competition with the natural product. It is extraordinary to see what a wide range so apparently simple a process covers, and how the latest refinements in the most remote fields of chemical industry have to be called in in order to perfect it.

Heumann's improved synthesis of indigo begins with the condensation of anthranilic with chloracetic acid to phenyl-glycine-*o*-carboxylic acid. The first condition of success was the cheap production of anthranilic acid from some substance which could be obtained in sufficient quantity. We need only consider the process which was ultimately adopted. This starts with naphthalene. This in itself was an enormous improvement on the older methods.

Naphthalene may be obtained in any quantity at a very low price. The amount of coal tar annually worked up for hydrocarbons (about two-thirds of the total production of coal tar) contains from 40,000–50,000 tons of naphthalene. It had long been a problem to find some use for the large quantities which are formed as a by-product in making benzene and toluene. It had been used to a small extent for increasing the illuminating power of coal gas (as 'albocarbon'), and there had been in recent years an increasing demand for it as a source of the new naphthalene azo-dyes. But the amount so employed was extremely small, and the greater part was used for purposes which returned only a minute profit, such as burning to make lampblack. The total quantity of naphthalene which was isolated annually was not more than 15,000 tons. There remained, therefore, the difference of 25,000 tons, at the lowest estimate, which could be isolated at the same price as that already on the market; and this was more than enough to supply the whole of the world's consumption of indigo.

Anthranilic acid is obtained from naphthalene through phthalic acid. This is converted into phthalimide, which, on treatment with chlorine and potash, goes, by a modification of Hofmann's reaction, into anthranilic acid. The reaction is most easily expressed if we suppose the phthalimide to act as the monamide of phthalic acid:—



The first problem was the oxidation of naphthalene to phthalic acid. The older method of using chromic acid was too expensive, and it was discovered that the oxidation could be performed by heating the naphthalene with sulphuric acid containing a high percentage of sulphur trioxide. But this would only be economical if some cheap method were found for preparing this acid, and for converting the sulphur dioxide which is formed in the reaction back into the trioxide. Such a method was the (then) new contact process of the Baden works, which is probably destined to supersede entirely the old lead-chamber process. This consists, of course, in mixing the gases from the pyrites burners with air, and passing them (after due purification) over platinized asbestos at a suitable temperature, whereby the sulphur dioxide combines with the oxygen of the air to form sulphur trioxide, which is absorbed in strong sulphuric acid. By this means it was easy, not only to prepare the original acid, but also to reoxidize the dioxide formed in the oxidation of the naphthalene. The process is in fact reduced to a cycle. The sulphur dioxide takes up the oxygen of the air and passes it on to the naphthalene. The importance of carrying on this cycle economically is shown by the fact that the annual production of phthalic acid leads to the formation of 35,000–40,000 tons of sulphur dioxide. If no substitute for the lead-chamber process had been discovered, it would have been impossible to produce indigo at a sufficiently low price to compete with the natural dye.

It is interesting to notice that the discovery that the addition of mercuric sulphate greatly facilitates the oxidation of the naphthalene by the sulphur trioxide was due to an accident. In one experiment the vessel in which the oxidation was being carried on contained an iron cup filled with mercury (no

doubt holding a thermometer). This was eaten through by the acid mixture, which came in contact with the mercury, and the yield was found to be much increased. This catalytic influence of the mercury, which occurs in other cases of sulphonation as well,[1] is remarkable, and a very probable explanation of it has been given by Dimroth.[2] He has shown that if a mercury salt is heated with an aromatic derivative, a compound is formed in which one hydrogen on the ring is replaced by mercury. This substitution is quite peculiar in that the position taken up by the mercury is not determined by the substituent already present: it is always ortho. Now it is found that if benzoic acid is sulphonated in the presence of mercury, the amount of meta and para acids produced is the same as if the mercury were not there; but in addition a considerable quantity of the *o*-sulphonic acid is formed, which is not obtained at all in the absence of mercury. This shows that the catalytic influence of the mercury is due to the formation and decomposition of a mercury derivative, as it introduces the sulphonic group at the position which the mercury (but no other substituent) would occupy.

The anthranilic acid having been obtained, it has to be combined with chloracetic acid: it was therefore necessary to improve the methods for preparing the latter. Acetic acid is, of course, easily obtained by the distillation of wood. Every year two million kilograms [3] of acetic acid are used for making indigo, and this quantity is got from more than 100,000 cubic metres of wood. In order to chlorinate this a large and cheap supply of fairly pure chlorine is required; and chlorine is also used for an earlier stage of the synthesis, the conversion of phthalimide into anthranilic acid. The ordinary processes for preparing chlorine were not found to be satisfactory; Weldon's was too expensive, and Deacon's gave too dilute a gas. The electrolytic method of preparation was finally adopted, but even here the gas required to be further purified by liquefaction.

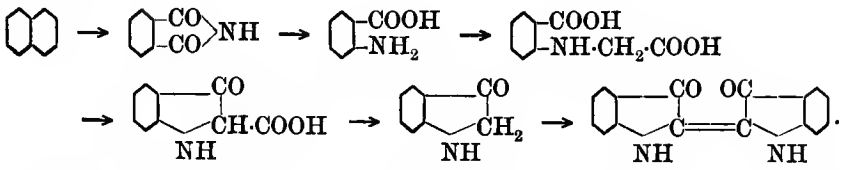
In this way the process of manufacture of synthetic indigo was ultimately perfected, and the cost of production reduced to (it is believed) less than a quarter of that of natural indigo.

A brief recapitulation of the method may be useful.

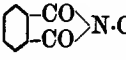
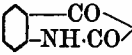
Naphthalene, obtained from coal tar, is oxidized to phthalic acid by heating with fuming sulphuric acid prepared by the contact process. The sulphur dioxide which is given off in this reaction is reconverted into sulphur trioxide by the same process. The phthalic acid is converted into phthalimide, and this by treatment with chlorine and soda (Hofmann's reaction) into anthranilic acid (*o*-amino-benzoic acid). The anthranilic acid is then condensed with chloracetic acid, which is made by chlorinating acetic acid obtained by the distillation of wood with chlorine produced by the electrolysis of sodium chloride and purified by liquefaction. The phenyl-glycine-*o*-carboxylic acid so obtained is fused with potash, which gives first indoxyl-carboxylic acid and then indoxyl. On treating the fused mass with water and exposing it to the air, the indoxyl

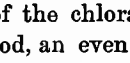
[1] e. g. anthraquinone, *C.* **04.** ii. 751; **05.** ii. 864.
[2] Dimroth, v. Schmaedel, *Ber.* **40.** 2411 (1907).
[3] In 1900: the amount must now be far greater.

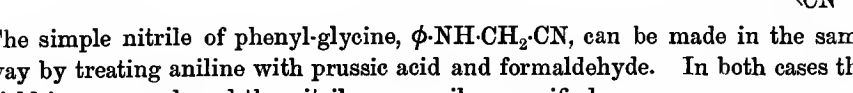
is oxidized to indigo. The more important stages are given in the following formulae :—



The advances which have been made in the preparation of synthetic indigo since the publication of Brunck's paper (1900) are not of a fundamental character.[1] Heumann's synthesis still holds its own, though it has been considerably modified, and there are now several rival processes in the field.

The earlier stages of Heumann's synthesis have not been altered, and are in fact very satisfactory as they stand. In the conversion of phthalimide into anthranilic acid two intermediate compounds have been isolated.[2] The first action of the chlorine is to form the imido-chloride,  , and this is converted by the alkali into  ; but nothing appears to be known as to how this change takes place.

The conversion of the anthranilic acid into phenyl-glycine-*o*-carboxylic acid by means of chloracetic acid gives unsatisfactory results, partly owing to the loss of carbon dioxide, and partly owing to the formation of the diacetic acid derivative,  . This is now avoided by not condensing the free acids but their alkaline salts, which are found to react completely in aqueous solution at 40° ; and the product, the acid salt of phenyl-glycine-carboxylic acid, being only slightly soluble, crystallizes out, and so is removed from the further action of the chloracetic acid. Although the yields obtained in this way are very good, an even better method has been worked out by Bender, which is based on Miller and Plöchl's [3] reaction of the anhydro-bases with formaldehyde and prussic acid. If the hydrochloride of anthranilic acid is treated in aqueous solution first with potassium cyanide and then with formaldehyde, the nitrile of phenyl-glycine-carboxylic acid separates out :—



The simple nitrile of phenyl-glycine, $\phi\cdot NH\cdot CH_2\cdot CN$, can be made in the same way by treating aniline with prussic acid and formaldehyde. In both cases the yield is very good, and the nitriles are easily saponified.

Of recent years, an increasing use has been made of the original form of Heumann's synthesis ; starting with aniline instead of anthranilic acid, and going through phenyl-glycine itself, instead of its carboxylic acid. The aniline and chloracetic acid are allowed to react in the presence of ferric oxide,[4] the

[1] For an account of the development of this industry up to 1904 see Reissert, *Zeit. f. angew. Chem.* **17.** 482.

[2] Bredt, Hof, *Ber.* **33.** 24, 27 (1900). [3] *Ber.* **25.** 2020 (1892). [4] *C.* **06.** ii. 1746.

glycine being thus removed as the insoluble ferric salt, and so protected from further action. The glycine can even be prepared by heating nitrobenzene with iron and chloracetic acid.[1]

For the condensation of the glycine to indoxyl derivatives Heumann uses potash fusion. The conversion of phenyl-glycine-carboxylic acid into indoxyl-carboxylic acid requires a temperature of 240–280°, and the yield, though fair, is not nearly quantitative. The analogous conversion of phenyl-glycine into indoxyl requires a higher temperature (300–350°), and the yield under ordinary circumstances is very small. It was this fact which prevented the method from being adopted at first. A large number of suggestions have been made for the improvement of the process, of which perhaps the most important is the addition of sodamide. In the presence of sodamide phenyl-glycine can be converted into indigo at a temperature of 180–240°, and the yields are much better. The sodamide is prepared by passing ammonia through liquid sodium. Its action is so energetic that it must be diluted with potash. The water evolved in the reaction liberates ammonia, and so the necessity of employing special means to exclude atmospheric oxygen is avoided. In this way it is possible to start with benzene, which, like naphthalene, can be obtained cheaply in any desired quantity. The sodamide is, of course, expensive; but in spite of this the method is used on the large scale by the Höchst dye works, while the Badische at Mannheim still keeps to Heumann's method, employing at the same time to some extent Bender's synthesis with formaldehyde and prussic acid.

Other suggestions for improving the yield in the potash fusion are the addition of alkaline earths,[2] of sodium oxide,[3] of magnesium nitride,[4] or of calcium carbide.[5] In all these cases the real point appears to be to secure the absence of water throughout the reaction. Instead of potash it is of advantage to use a mixture of potash and soda in molecular proportions, on account of its lower melting-point. It is also found that the yield is increased if ammonia is passed over or through the fused mixture[6]; other gases such as hydrogen, nitrogen, coal gas, or the vapour of hydrocarbons may be used instead with the same results.[7]

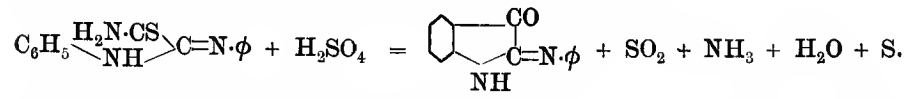
An essentially new and practicable synthesis has been published by Sandmeyer.[8] He starts with thiocarbanilide, which when warmed in aqueous alcohol to 50–60° with potassium cyanide and white lead (basic lead carbonate) loses hydrogen sulphide to form carbo-diphenyl-imide, which then adds on prussic acid:—

$$\begin{matrix}\phi\cdot NH\\ \phi\cdot NH\end{matrix}\!\!>\!CS \rightarrow \begin{matrix}\phi\cdot N\\ \phi\cdot N\end{matrix}\!\!>\!C \rightarrow \begin{matrix}\phi\cdot NH\\ \phi\cdot N\end{matrix}\!\!>\!C\cdot CN.$$

If the product is treated with yellow ammonium sulphide for two days at 25–35°, it is converted into the thio-amide, $\begin{matrix}\phi\cdot NH\\ \phi\cdot NH\end{matrix}\!\!>\!C\cdot CS\cdot NH_2$. This thio-amide

[1] *C.* **06.** ii. 1700.
[2] *C.* **07.** i. 383.
[3] *C.* **06.** i. 514.
[4] *C.* **06.** i. 617.
[5] Ibid.
[6] *C.* **06.** i. 618.
[7] *C.* **07.** i. 435, 519.
[8] *Zeit. Farb. u. Text.* **2.** 129 (1903).

is then heated with concentrated sulphuric acid at 95–110° till no more sulphur dioxide is evolved, whereby α-isatin-anilide is produced :—



The α-isatin-anilide, when heated with dilute mineral acids, splits up into aniline and isatin, while on warming with yellow ammonium sulphide it is readily reduced to indigo. In practice the solution of the anilide in concentrated sulphuric acid is allowed to flow directly into water, simultaneously with a dilute solution of sodium hydrogen sulphide. α-Thio-isatin, , is precipitated; and this when treated with alkali or alkaline carbonate gives a mixture of indigo and sulphur.

This synthesis of indigo is somewhat complicated ; but the yields at each stage are so good, and the original materials so cheap, that it is quite possible that it may become a serious rival to the Heumann process.

The introduction of artificial indigo at first met with various difficulties, the chief of which was, as Brunck points out, that the general public are quite incapable of understanding what is meant by a chemical individual. They could not realize that the synthetic and the natural products were (except for the impurities of the latter) identical, and insisted on regarding the one as an inferior substitute for the other. But these objections are rapidly disappearing. The synthetic indigo is purer than the natural, and of far more constant composition, which makes it much easier to use ; and above all its cost price is far lower. The annual value of the indigo produced in India before 1897, when the first artificial indigo was placed on the market, was about three millions sterling. By 1902 it had fallen to one and a quarter millions. This was partly due to a decrease in the amount produced, but largely to the remarkable fall in the price. The price of indigo before 1896 was about £600 per metric ton. By 1900 it had fallen to £250, and by 1905 to £115. These latter figures refer to the synthetic product: the natural is still somewhat more expensive. This great fall in price has naturally led to a great increase in consumption ; and the decrease in the production of the natural dye has been far more than counterbalanced by the enormous increase in the manufacture of the artificial. In 1900 the world's production of indigo was about 5,000 tons ; in 1905 the amount exported from Germany was over 11,000 tons, to which the still considerable Indian production has to be added, as well as the consumption within Germany itself. The whole amount cannot fall far short of 20,000 tons.

Before we leave the subject of indigo, it is interesting to notice the scientific advances, both theoretical and practical, which arose more or less directly through the investigation of the constitution and syntheses of the compounds of this group.

The method of reduction by passing the vapour of the substance over heated zinc dust was discovered by Baeyer in 1866 in his endeavours to reduce oxindol to indol ; it immediately afterwards led Graebe and Liebermann to the synthesis of alizarine, and has subsequently been most widely extended.

Another very important method of reduction—the use of sodium and boiling amyl alcohol—was invented by Baeyer in 1879 for the reduction of dichlorindol to indol at a lower temperature than that required by the zinc method, in order more completely to exclude the possibility of intramolecular change.

Again, to take theoretical questions, it was from the study of the ring-formation in the syntheses of the indol derivatives that Baeyer came to the conclusion, in 1880, that such closing of the ring only occurs when by its means a ring of either five or six atoms is produced; and it was in the development of the views thus originated that he was led to formulate his theory of strain in 1885.

Finally, his investigation of isatin revealed, in 1882, three years before the first of Laar's classical papers appeared, one of the earliest clearly recognized cases of tautomerism; and it was in connexion with this that he gave, in 1883, the first distinct expression of his view that the peculiar behaviour of a tautomeric substance is due to the mobility of a hydrogen atom which can migrate, according to circumstances, from one position to another; whereas in its two stable series of derivatives this hydrogen atom is replaced by other and heavier groups, which do not possess the same mobility.

CHAPTER XVIII

6-RINGS: C_5N

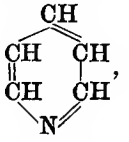
Of these bodies, as of the 5-rings, only a single class will be discussed, the derivatives of a ring of five carbon atoms and one nitrogen, comprising the pyridine, quinoline, and isoquinoline groups.

1. PYRIDINE

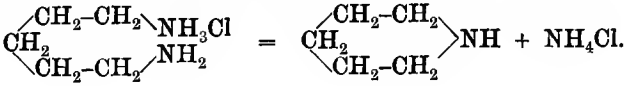
The discovery of pyridine is due to Anderson, who in 1845–51 succeeded in isolating it from bone oil, together with picoline (methyl-pyridine) and lutidine (dimethyl-pyridine): the three names were invented by him. The pyridine bases have since been found to occur in the products of distillation of almost all kinds of nitrogenous matter, and the source from which they are now usually prepared is coal tar. It is to be noticed that their formation from animal matter requires the presence of unsaponified fats. If the fats are removed, pyrrol compounds are formed, but no pyridines; while if free fatty acids are present, they are converted into the corresponding nitriles. It would seem therefore that the production of pyridine derivatives only occurs in the presence of glycerine. This is converted at the high temperature into acrolein and similar aldehydes, which combine with the ammonia formed from the nitrogenous matter (gelatine, &c.) to give pyridine bases.

As regards the formula of pyridine, we have as usual two questions to consider. It is easy to show that it contains a ring of five carbons and one nitrogen, with one hydrogen on every carbon; but this leaves six valencies to be accounted for, about which there has been much dispute.

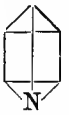
In 1869 Körner proposed for pyridine a formula,

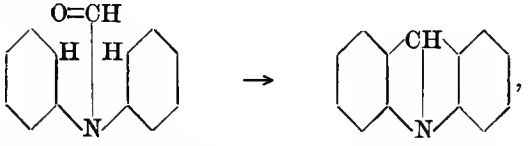


which is that of benzene with one CH replaced by N. Whether this is correct as to the six extra valencies or not, it certainly is so as to the arrangement of the atoms. The various pyridine syntheses afford many proofs of this: the simplest and most important is given by the preparation from pentamethylene-diamine. The hydrochloride of this base on heating loses ammonium chloride to give piperidine, whose formula is thus established:—



Piperidine is readily oxidized (by heating with concentrated sulphuric acid, nitrobenzene, or silver acetate) to pyridine, which thus must have the arrangement of atoms which Körner supposes.

Körner's formula obviously corresponds to Kekulé's benzene formula; and, as with benzene, a variety of other arrangements of the six internal valencies have been suggested. Riedel's, in which the nitrogen is united to three different carbon atoms,  , is supported by a certain amount of evidence, especially by the various reactions and syntheses of acridine (which is undoubtedly dibenzopyridine), which point to para-linkage: in particular by its formation from formyl-diphenylamine:—



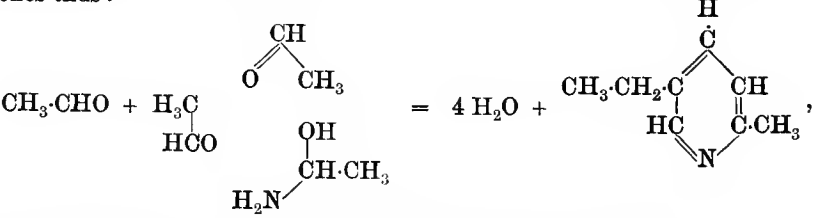
Formyl-diphenylamine. Acridine.

This peculiarity of acridine is exactly parallel to that of anthracene, where the same question of para-linkage arises. And therefore as with benzene we accept Kekulé's structure, so with pyridine we may take Körner's as the most probable: in both cases with Thiele's interpretation.

The equivalence of the α- and α'-positions in pyridine has been proved (if the proof is of any value) by synthesizing α-phenyl-α'-tolyl and α-tolyl-α'-phenyl pyridine, which were found to be identical.[1]

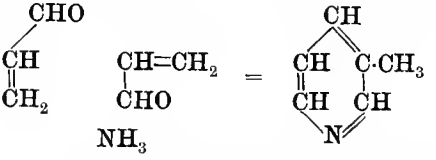
The syntheses of pyridine derivatives are numerous. The following are among the most important:—

Aldehyde ammonias condense with themselves or with other aldehydes or ketones thus:—



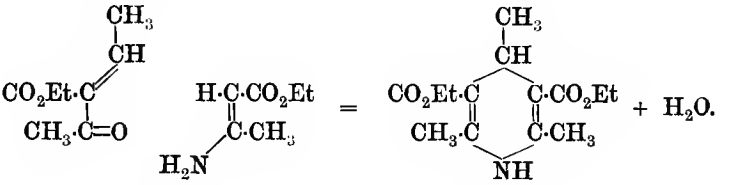
the product being α-methyl-β'-ethyl pyridine, known as aldehyde collidine.

A similar reaction is the formation of picoline by the condensation of glycerine with ammonia, to which its production in the dry distillation of animal substances is no doubt due. The glycerine first gives acrolein:—

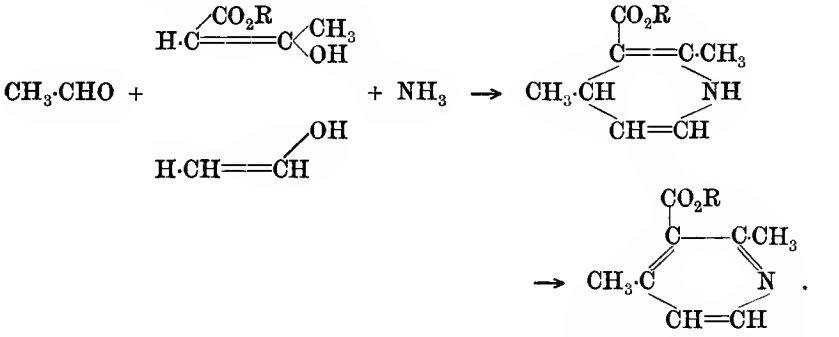


[1] Scholtz, Wiedemann, *Ber.* **36.** 845 (1903).

Secondly, there is Hantzsch's synthesis from β-diketo-compounds or ketonic esters with aldehydes and ammonia. This gives dihydro-pyridine derivatives: e. g. dihydro-collidine dicarboxylic ester from acetaldehyde and acetoacetic ester. The reaction has been further investigated by Knoevenagel,[1] who finds that it takes the following course. The aldehyde and the ammonia combine to form aldehyde ammonia; this reacts with a molecule of acetoacetic ester to form ammonia and ethylidine acetoacetic ester, $CH_3{\cdot}CO{\cdot}C{\cdot}CO_2Et$ (with $CH{\cdot}CH_3$). The ammonia then acts on another molecule of acetoacetic ester, forming β-amino-crotonic ester, $CH_3{\cdot}C(NH_2){=}CH{\cdot}CO_2Et$. Finally, one molecule of each of these products condenses to give the dihydro-collidine derivative:—



This is the reaction which occurs when the acetoacetic ester is in excess; but a different, though similar, product is obtained if the aldehyde is in excess. In this case an unreduced pyridine derivative is formed. The simplest explanation is that two molecules of aldehyde condense with one of acetoacetic ester and one of ammonia to a dihydro-compound, and then this is oxidized by excess of aldehyde to a simple pyridine:—

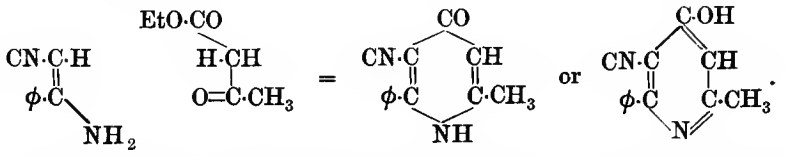


α-γ-dimethyl-pyridine-β-carboxylic ester.

A remarkable synthesis has been discovered by E. v. Meyer,[2] which starts from the so-called benzo-aceto-dinitrile. This is an unsaturated amino-nitrile formed by the addition of benzonitrile to acetonitrile under the influence of sodium (by a sort of polymerization). It will condense with acetoacetic ester in

[1] *Ber.* **31.** 745 (1898); cf. Beyer, *Ber.* **24.** 1662 (1891).
[2] *C.* **05.** i. 262.

presence of hydrochloric acid to give a cyan-hydroxy-pyridine (or, in the tautomeric form, pyridone):—



The synthesis from pentamethylene-diamine through piperidine has already been given; and also that from potassium pyrrol and chloroform or methylene iodide.

The pyridine bases are colourless liquids of peculiar smell. Pyridine itself is miscible with water, but the higher homologues rapidly become less soluble, and are generally more soluble in cold water than hot.

Pyridine boils at 115·2°. It is a weak base of about the strength of aniline[1]; but it is much stronger than pyrrol, and forms fairly stable salts. It is not unfrequently used in order to bring about reactions which involve the separation of hydrochloric or hydrobromic acid, the reaction being sometimes carried out in pyridine solution. It would seem that this action does not merely depend on the basic character of pyridine; but it is not properly understood.[2] Thus it has been used for benzoylation[3]; the benzoyl chloride is dissolved in pyridine (which causes great evolution of heat, suggesting the formation of some compound), and the amine, amide, or alcohol is added. Again, pyridine (or quinoline) will remove hydrobromic acid, for example, from bromo-succinic ester, giving fumaric ester[4]; and this has the advantage over the use of alkali that the ester group is not saponified. Pyridine forms an efficient carrier in the chlorination and bromination of aromatic hydrocarbons,[5] and it also acts as a catalyst (as does quinoline) in promoting both the Claisen reaction and the formation of Grignard's reagent.[6]

As we should expect from the formula, the derivatives of pyridine exhibit the aromatic character in a very high degree. This is shown even in their physical properties—the small molecular volume and the high refractive power—and also in their very remarkable stability. Pyridine is even more stable than benzene. It resembles benzene in not being oxidized by chromic acid or fuming nitric acid; and that it is still more stable than benzene is shown by the fact that when phenyl-pyridine is oxidized, it is the benzene and not the pyridine nucleus that is destroyed, the product being pyridine carboxylic acid.

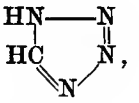
It has recently been found, however, that the pyridine can be broken between the nitrogen and the carbon by several somewhat unexpected reagents: for example, by dichloro-nitrobenzene (Zincke), by cyanogen bromide (Königs), and,

[1] Constam, White, *Am. Ch. J.* **29**. 1 (*C.* **03**. i. 523).
[2] Cf. Eckstein, *Ber.* **39**. 2135 (1906).
[3] Freundler, *C. R.* **136**. 1553; **137**. 712; *Bull. Soc.* [3] **31**. 616 (1903, 1904).
[4] Dubreuil, *C. R.* **139**. 870 (*C.* **05**. i. 25). [5] Cross, Cohen, *Proc. C. S.* **24**. 15 (1908).
[6] Tingle, Gorsline, *Am. Ch. J.* **37**. 483 (*C.* **07**. ii. 30).

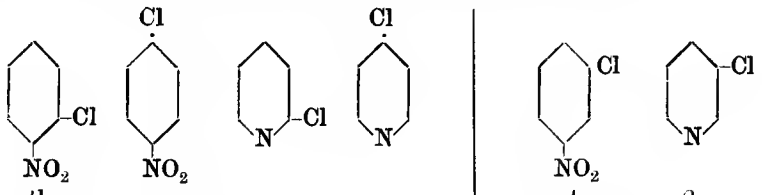
what is more remarkable, by sodium bisulphite, an intermediate addition-compound being formed in this case.[1]

As in the benzene series, the homologues of pyridine are easily oxidized by strong oxidizing agents (especially potassium permanganate), the side chains, whatever their length, being converted into carboxyl.

Almost the only reactions of which pyridine is capable are substitutions, and these occur less readily than with benzene. The halogens substitute more or less easily, sulphuric acid only at a high temperature, and nitric acid usually not at all. Marckwald [2] has advanced a theory to account for this latter phenomenon, as well as certain other peculiarities of pyridine. He points out that a nitrogen atom in a ring is able to behave under certain circumstances as a strongly negative group. For example, tetrazol,



is an acidic compound which reddens blue litmus. This is not necessarily incompatible with the nitrogen also possessing basic properties, i. e. the power of becoming pentad. In the compounds in which it remains triad and exhibits its negative character, it behaves like a carbon atom in the benzene ring attached to a strongly negative substituent, e. g. C·NO_2. Thus, if pyridine is substituted the substituent takes up the β-position, as nitrobenzene gives meta-di-derivatives. Again, in the chloro-pyridines we find the α- and γ-chlorine extremely mobile—easily replaced by NH_2—as in *o*- and *p*-chloro-nitrobenzene, whereas in β-chloro-pyridine, as in *m*-chloro-nitrobenzene, it is very firmly attached:—



ortho para α- γ- meta β-

Labile. Stable.

Again, the repellent influence of this negative nitrogen explains why it is so difficult to introduce into pyridine negative substituents like SO_3H and NO_2. But if the acidifying influence of the nitrogen is diminished by the introduction of a basic group, nitration becomes possible; amino-pyridine can be nitrated directly. This, however, is a general characteristic of aromatic NH_2.

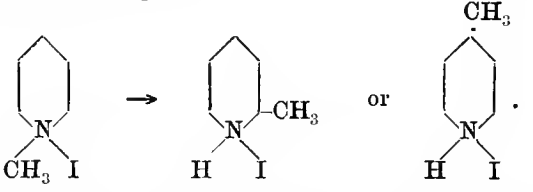
Although pyridine is so stable a compound it is comparatively easily reduced. When treated with sodium and alcohol in the cold, it takes up six hydrogen atoms and forms piperidine. Here, again, we may compare its behaviour with that of certain negatively substituted benzenes, namely, the carboxylic acids, which can easily be made to take up two or four hydrogen atoms in the cold. On the other hand, it is remarkable that if the vapour of pyridine mixed with hydrogen is passed over heated nickel, no piperidine is formed at any tempera-

[1] Bucherer, Schenkel, *Ber.* **41.** 1346 (1908). [2] *Ber.* **26.** 2187 (1893); **27.** 1317 (1894).

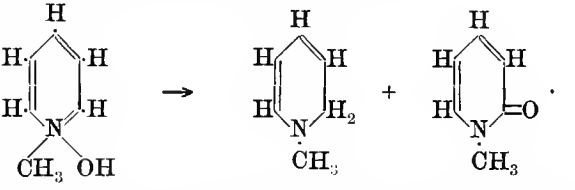
ture.[1] Below 220° normal amylamine is produced; while above 220° the nitrogen is split off from the carbon in both sides, with the formation of ammonia and pentane. The absence of piperidine is due to the fact that the reverse action takes place much more easily: if piperidine vapour is passed over heated nickel it breaks up into pyridine and hydrogen.

Pyridine is also capable of addition to the nitrogen, which becomes pentad. The pyridine compounds are, as has been pointed out, moderately strong bases, though weaker than the reduced compounds, such as piperidine. They form fairly stable salts with one equivalent of acid, and also characteristic gold and platinum double salts. They further combine directly with any metallic salts in the same way as ammonia.

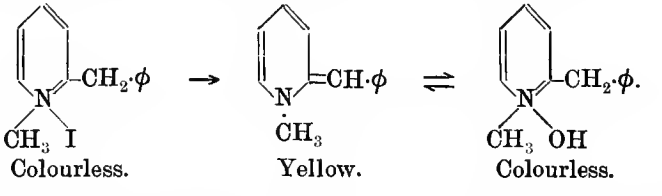
They are also able to add on alkyl iodide to form the pyridinium derivatives, which undergo three remarkable changes. On heating, the alkyl group migrates to the α- or γ-position on the ring, as in Hofmann's aniline reaction, where the *o*- and *p*-positions are taken up:—



On treatment with silver hydrate the pyridinium iodides yield strongly basic hydroxides (resembling the quaternary ammonium bases), and when these are warmed the oxygen migrates to the carbon. The reaction is complicated, but apparently gives a dihydro-pyridine and a pyridone:—



This behaviour is common with hydroxyl attached to doubly linked pentavalent nitrogen; as we have seen in the triphenyl-methane dyes, and the diazonium hydroxides. The quaternary bases formed by the addition of methyl iodide to α- or γ-alkyl pyridines, which, like the others, are colourless, when treated with soda lose hydriodic acid and are converted into bright yellow so-called pyridane compounds.[2] On dilution, or on dissolving the compound in pure water, the colour disappears again; water is added on and the quaternary hydroxide formed:—

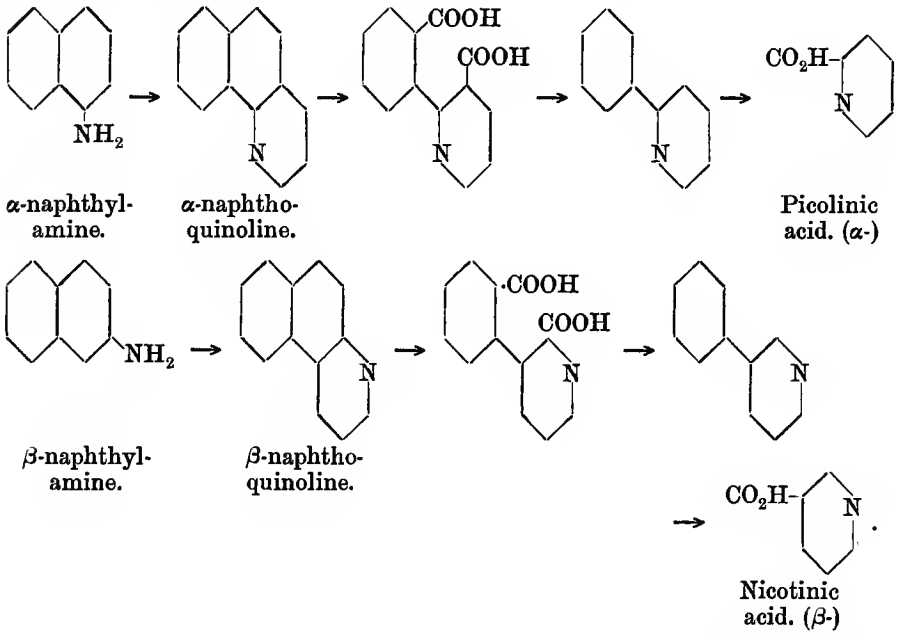


[1] Sabatier, Mailhe, *C. R.* **144.** 784 (*C.* **07.** ii. 73).

[2] Decker, *Ber.* **38.** 2493 (1905).

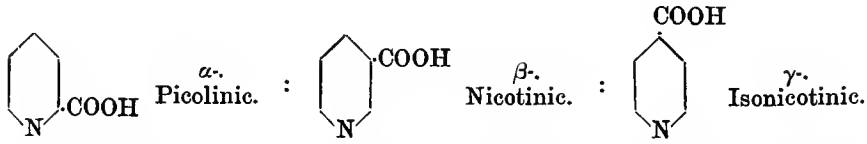
This curious reaction, with its characteristic change of colour, also occurs in the quinoline and isoquinoline series, and in compounds in which the nitrogen is replaced by oxygen or sulphur, such as the xanthones and thio-xanthones.

The determination of position among the pyridine derivatives is carried out as follows: The mono-derivatives (omitting the N-compounds, which obviously belong to a different class) are of three kinds, α-, β-, γ-, as required by the formula. The position is determined by reference to the three monocarboxylic acids, which are known respectively as picolinic, nicotinic, and isonicotinic acids, and whose constitution has been made out by Skraup. The starting-point is the naphthoquinolines, which are obtained by a modification of the well-known Skraup synthesis of quinoline—from α- and β-naphthylamine respectively. This reaction, the details of which will be discussed later, consists in condensing an aromatic amine with glycerine, the 3-carbon chain joining up with the nitrogen of the NH_2 to form a 6-ring. Since both α- and β-naphthylamine give in this reaction compounds undoubtedly containing a pyridine nucleus, there can be no doubt about their formulae:—

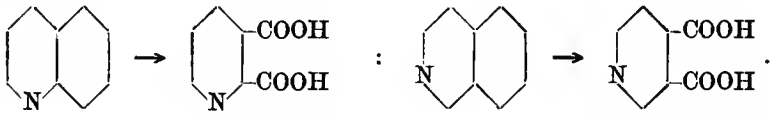


On oxidizing these two naphthoquinolines, they both split the middle ring to give phenyl-pyridine dicarboxylic acids, which lose two molecules of carbon dioxide to form phenyl-pyridines. Now it is obvious from the formulae that α-naphthoquinoline must give α-phenyl-pyridine, and the β-compound β-phenyl-pyridine. Finally on oxidation the phenyl group is destroyed, only carboxyl remaining. Hence we know that the resulting pyridine monocarboxylic acids must be α- and β- respectively. And it is found that the acid obtained from α-naphthylamine is picolinic, which must therefore be the α-, and that from β-naphthylamine, which must be the β-, is nicotinic. The third acid, isonico-

tinic, which is got from the third isomeric phenyl-pyridine, must therefore be the γ-carboxylic acid:—



A rather neater method of orienting these acids depends on the following reactions. Quinoline and isoquinoline, whose formulae are proved by their syntheses, both give on oxidation dicarboxylic acids of pyridine. Quinoline gives quinolinic acid, which thus has the carboxyls in the α- and β-positions, and isoquinoline gives cinchomeronic acid, where the positions must be β- and γ-:—



Quinolinic acid (α,β). Cinchomeronic acid (β,γ).

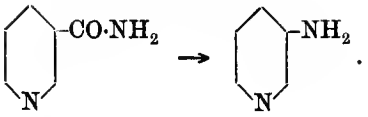
Both these acids can be made by heating to lose one molecule of carbon dioxide, leaving monocarboxylic acids. Quinolinic gives only one such acid, nicotinic, and cinchomeronic a mixture of nicotinic and isonicotinic. Hence nicotinic acid, which is given by both, must have the carboxyl in the position common to both, that is, the β-position. Isonicotinic acid, on the other hand, must retain the other carboxyl of cinchomeronic acid, that is, it must be the γ-acid.

The orientation of the di-substitution-products of pyridine is fixed by reference to the six dicarboxylic acids, whose constitution has been determined by Ladenburg by a similar method.

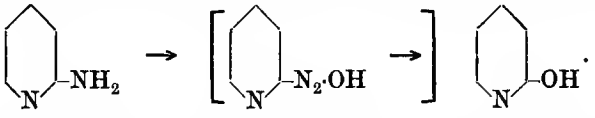
It is remarkable that while the carboxylic acids of pyridine and quinoline, and their esters, amides, and nitriles, resemble the corresponding derivatives of benzene, the acid chlorides are quite different. They do not dissolve in organic solvents except when they react with them, their melting-points are very high, lying near those of the hydrochlorides of the acids, and they are marked by great stability and the absence of smell. These peculiarities suggest that they are really polymers of the acid chlorides; but as no solvent can be found in which to determine their molecular weight, this question cannot be settled.[1]

The amino-derivatives of pyridine have a somewhat singular behaviour. The α- and γ- may be obtained, as we have seen, by treating the corresponding chlorine compounds with ammonia. The β-derivative cannot be prepared in this way, as the chlorine is too firmly attached. It is therefore necessary to use an indirect method, that by which the amino-pyridines were first obtained. This is by means of the Hofmann reaction, the amide of nicotinic acid being converted by bromine and soda into β-amino-pyridine:—

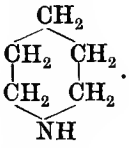
[1] H. Meyer, *Ber.* **38.** 2488 (1905).



The β-amino-compounds, in which, as in the meta-derivatives of nitrobenzene, the negative influence of the nitrogen on the NH_2 is least, behave, as is to be expected, like aromatic amines ; they give with nitrous acid diazo-compounds, which form diazo-amino-bodies and azo-dyes. But the behaviour of the α- and γ-amines is peculiar. In dilute acid solution nitrous acid has no action on them at all. In concentrated sulphuric acid they can be diazotized, but the diazo-compounds cannot be isolated ; if the sulphuric acid solution is poured on ice, the diazo-nitrogen is evolved quantitatively, and the oxy-pyridine formed :—

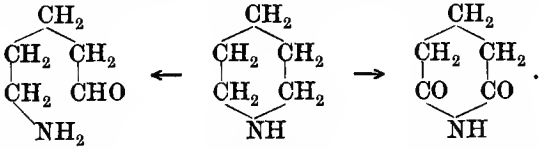


Of the reduction-products of pyridine the most important is piperidine or hexahydropyridine,



It is to be noticed, however, that in this series the tendency to form the hexahydro-compound on reduction is less marked than usual. Thus it is much easier to obtain the di- and tetrahydro-compounds directly than with the benzene derivatives, where it is scarcely possible to stop short of complete reduction.

Piperidine is a colourless liquid boiling at 106°, which is miscible with water. It can be obtained from pepper, whence the name. Its formation by heating the hydrochloride of pentamethylene diamine (or ϵ-chloramylamine) has already been mentioned, and also the ease with which it can be oxidized to pyridine. It is a strong base. The ring is weakened by the reduction,[1] and can be broken by a variety of reagents. Thus oxidation with hydrogen peroxide converts it partly into glutarimide (to which it bears the same relation as tetrahydropyrrol to succinimide) and partly to δ-amino-valerianic aldehyde :—



δ-amino-valerianic aldehyde. Piperidine. Glutarimide.

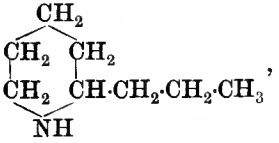
[1] The same is the case with the tetrahydro-derivatives. Cf. Lipp, Widnmann, *Ber.* **38.** 2471 ; Wallach, ibid. 2803 (1905).

ALKALOIDS

Among the compounds of the pyridine group which are found in nature are several important members of the class of alkaloids. The alkaloids are defined by Ladenburg[1] as 'those naturally occurring vegetable substances of basic character which contain at least one nitrogen atom forming part of a heterocyclic ring'. These bodies[2] are of great interest from many points of view, and especially as providing examples of the methods used in determining the formulae of bodies of natural origin, that is, bodies whose origin gives us no clue to their structure. The most important alkaloids of the pyridine group are coniine, piperine, and nicotine.

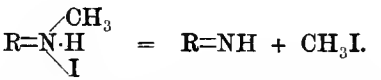
Coniine

Coniine, dextro-*α*-*n*-propyl-piperidine,



is of interest as the first alkaloid whose synthesis was successfully carried out, owing no doubt to its comparatively simple structure. Coniine occurs in hemlock (*Conium maculatum*, whence the name), especially in the seeds, together with several other alkaloids. It is a colourless liquid boiling at 167°, which has a strong smell and is a violent poison. It was discovered in hemlock seeds by Giesecke in 1827 ; its correct molecular formula, $C_8H_{17}N$, was established in 1881 by Hofmann, who also succeeded in throwing much light on its structure; and its synthesis was carried out by Ladenburg in 1886. In investigating its formula Hofmann made use for the first time of his method of exhaustive methylation.[3] This reaction has already been mentioned; but it is so important for determining the structure of alkaloids that it is worth considering more in detail.

If a quaternary ammonium halide is heated, it splits off the halogen together with the smallest of the alkyl groups. The same occurs with the halide of a tertiary base ; and this fact has been made use of in the case of the alkaloids.[4] When the hydriodide of a base with a methyl on the nitrogen is heated, it forms methyl iodide:—



The methyl iodide can then be determined, as in Zeisel's method, with alcoholic silver nitrate.

[1] Ann. **301.** 117 Anm.

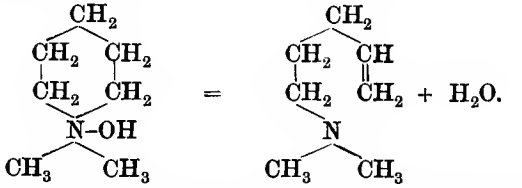
[2] See J. Schmidt, *Konstitution der Pflanzenalkaloide*, 1904; *Die Alkaloidchemie in d. Jahren* 1900–1904 (Enke, Stuttgart).

[3] *Ann.* **78.** 263; *Ber.* **14.** 494, 659 (1881).

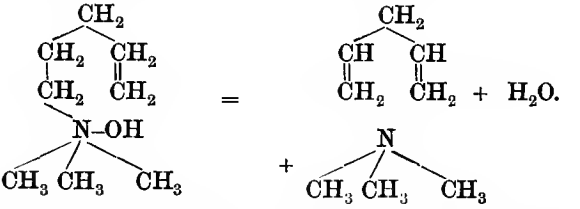
[4] Herzig, H. Meyer, *Mon.* **15.** 613 (1894); **16.** 599 (1895); **18.** 379 (1897).

But if the halogen of a quaternary halide is replaced by hydroxyl, and this body is heated, then it is the largest of the alkyl groups which splits off from the nitrogen. This is the foundation of the method of exhaustive methylation, which was discovered by Hofmann, and fully explained some time later by Ladenburg.

In the case of an alkaloid, where the nitrogen forms part of a ring, the largest hydrocarbon radical is of course the ring itself. When the quaternary hydroxide is heated, this breaks off from the nitrogen on one side, but still remains attached on the other. The result is that only a molecule of water is lost, and a base with the same number of carbon atoms remains. For example, with piperidine :—



The product adds on another molecule of methyl iodide, and the corresponding hydroxide when heated separates the nitrogen from the long chain altogether, giving a hydrocarbon piperylene, C_5H_8. The reaction is most naturally represented thus :—



This must undoubtedly be the formula of the primary product, and was for a long time supposed to be that of piperylene itself. But certain peculiarities in its behaviour led Thiele[1] to doubt this, and he has been able to show that its true formula is $CH_2{=}CH{\cdot}CH{=}CH{\cdot}CH_3$. One of the strongest proofs is its reaction with potassium permanganate. This must break the chain at the double bonds; and di-vinyl-methane would give formic and malonic acids: whereas the actual products from piperylene are formic and acetic acids. It is evident that the di-vinyl-methane first formed undergoes a rearrangement, no doubt under the influence of the simultaneously produced trimethylamine, which exerts a similar effect on the unsaturated lactones.[2]

This intramolecular change, however, does not affect the value of the reaction, which essentially consists in splitting out the nitrogen from the ring of which it forms part, and hence enables us to determine what the nature of that ring was: a point of the utmost importance in investigating a class of bodies like the alkaloids, whose origin leaves us quite in the dark as to the type of compounds to which they may belong.

It has recently been discovered that if the compound contains methoxyl groups, as many alkaloids do, these are converted by the action of the methyl

[1] *Ann.* **319.** 226 (1901). [2] Ib. 129.

iodide into hydroxyls, so that a certain caution is necessary in employing the method in these cases.[1]

In the case of coniine, which contains no oxygen, we do not meet with any such difficulties. When coniine is subjected to this treatment, Hofmann showed that it passes through the following stages :—

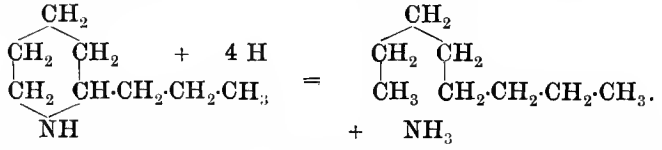
$$C_8H_{17}N \rightarrow C_8H_{16}(CH_3)NI \rightarrow C_8H_{16}(CH_3)N\cdot OH \rightarrow C_8H_{15}(CH_3)_2N$$

Coniine.

$$\rightarrow C_8H_{15}(CH_3)_3N\cdot OH \rightarrow \underset{\text{Conylene.}}{C_8H_{14}} + N(CH_3)_3 + H_2O.$$

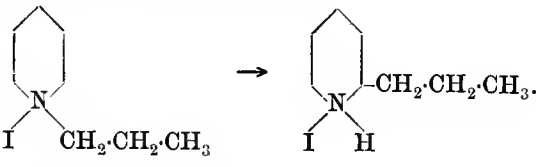
The resulting hydrocarbon differs from piperylene, as coniine does from piperidine, by C_3H_6. Hofmann therefore suggested that coniine was a homologue of piperidine, and soon after Königs proposed for it the formula of a propyl-piperidine, though there was as yet no evidence as to the disposition of the three extra carbon atoms.

Königs' view was completely confirmed by the very unexpected results which Hofmann obtained when he distilled coniine hydrochloride with zinc dust.[2] His object was to reduce it ; but instead of this, he found that the coniine lost six atoms of hydrogen, and gave a base of the formula $C_8H_{11}N$, which he called conyrine. This was easily shown to be a pyridine derivative, and on oxidation gave picolinic acid (pyridine α-carboxylic acid). It therefore only contained one side chain, and that in the α-position. It followed that conyrine was α-propyl- or α-isopropyl-pyridine, and coniine, containing six hydrogen atoms more, was α-propyl- or α-isopropyl-piperidine. That it was a propyl and not an isopropyl compound was rendered very probable by Hofmann's further discovery [3] that coniine on reduction with hydriodic acid is converted into ammonia and normal octane, which indicates that it contains an unbranched chain of carbon atoms :—



The question was finally set at rest by Ladenburg's synthesis of coniine in 1886.[4]

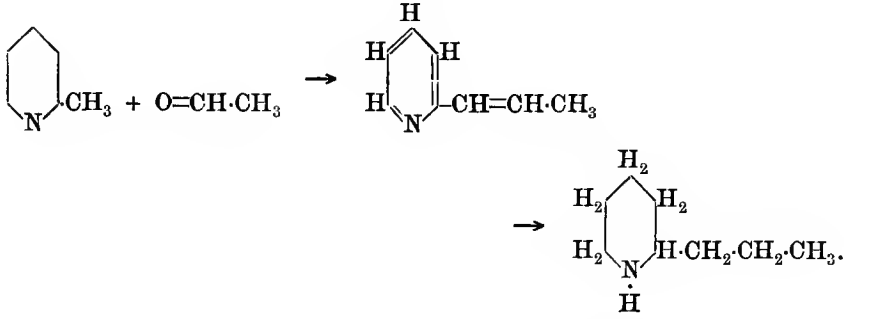
The first point was to prepare α-propyl-pyridine. This he endeavoured to do by heating propyl-pyridinium iodide. As we have seen, the alkyl-pyridinium iodides when heated change into C-alkyl-pyridines, the alkyl taking the α- or γ-position ; and so it should have been possible to obtain normal propyl-pyridine from normal propyl-pyridinium iodide :—



[1] Freund, Becker, *Ber.* 36. 1523 (1903).
[2] *Ber.* **17.** 825 (1884).
[3] *Ber.* **18.** 13 (1885).
[4] *Ber.* **22.** 1404.

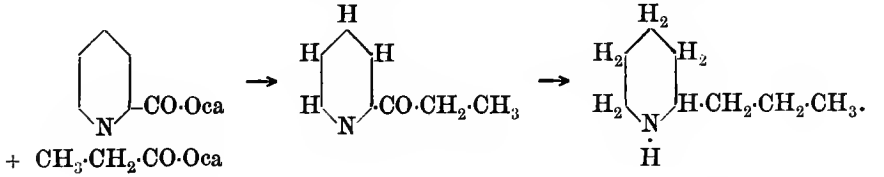
It was found, however, that whether you start with normal or isopropyl-pyridinium iodide, the same product is formed,[1] and this will not yield coniine, because, as was afterwards discovered, it is the isopropyl compound: the alkyl undergoing a rearrangement in the course of its migration.

The method by which Ladenberg finally succeeded in preparing the normal propyl compound was to condense α-picoline (α-methyl-pyridine) with paraldehyde, by heating under pressure. This gives α-allyl-pyridine; and when this is reduced with sodium in alcoholic solution, the allyl group is converted into normal propyl, and at the same time the pyridine ring is reduced to piperidine:—



In this way he obtained α-*n*-propyl-piperidine. But as this contains an asymmetric carbon atom, the product is of course a mixture of the dextro- and laevo-forms. If its salt with dextro-tartaric acid is recrystallized from water, the salt of the dextro-base separates out first, and when this is treated with alkali it gives the dextro-α-*n*-propyl-piperidine, which was shown to be identical with the natural coniine. As this was the first synthesis of a natural alkaloid, it is worth pointing out that it is a complete one; that is to say, it makes it possible to prepare coniine from its elements. The preparation of aldehyde, *d*-tartaric acid, and glycerine from their elements is sufficiently obvious; from glycerine to α-picoline the stages are: allyl bromide, trimethylene bromide, pentamethylene-diamine, piperidine, pyridine, pyridine methyl iodide, α-picoline.

A different synthesis of coniine has since been carried out by Engler.[2] He distilled the calcium salt of picolinic acid with calcium propionate, and so got α-ethyl-pyridyl ketone. On energetic reduction of this with sodium and alcohol, the ketone group is converted into CH_2, and also the ring reduced to piperidine, and thus α-*n*-propyl-piperidine, that is, inactive coniine, is obtained:—



[1] Ladenburg, *Ber.* **18.** 1587 (1885).

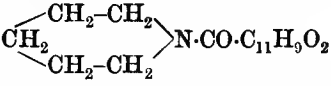
[2] *Ber.* 24. 2530 (1891).

Piperine

Piperine occurs in the seeds of various kinds of pepper. Its formula is $C_{17}H_{19}NO_3$. When it is boiled with alcoholic potash it takes up a molecule of water, and is converted into piperidine and a monobasic acid known as piperinic acid[1]:—

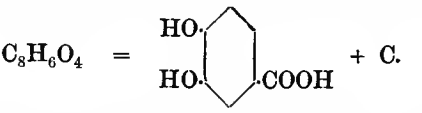
$$\underset{\text{Piperine.}}{C_{17}H_{19}NO_3} + H_2O = \underset{\text{Piperidine.}}{C_5H_{11}N} + \underset{\text{Piperinic acid.}}{C_{12}H_{10}N_4}.$$

The reverse change occurs when the acid chloride of piperinic acid is heated with piperidine, piperine being formed.[2] It follows that piperine must be a kind of amide of piperidine with piperinic acid, and must contain the group

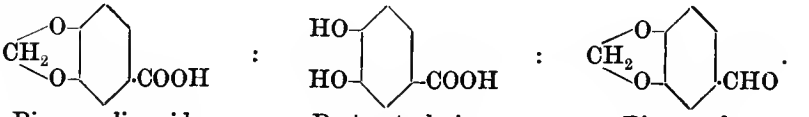


Hence it only remains to determine the formula of piperinic acid.

This was done by Fittig. He showed in the first place that when piperinic acid is oxidized with potassium permanganate, it gives first an aldehyde, piperonal, and then the corresponding acid, piperonylic acid, $C_8H_6O_4$. This last acid when heated with hydrochloric acid is converted with separation of carbon into protocatechuic acid, which was shown to be 3,4-dihydroxy-benzoic acid:—

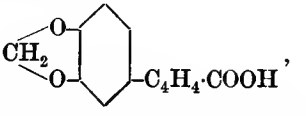


Since this acid can be reconverted into piperonylic acid by heating with methylene iodide and alkali, the latter must be the methylene ether of protocatechuic acid, and piperonal the corresponding aldehyde, the methylene ether of protocatechuic aldehyde:—



Piperonylic acid. : Protocatechuic acid. : Piperonal.

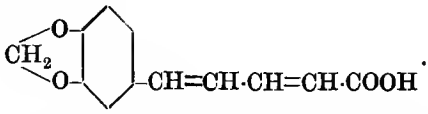
Now piperonylic acid is got from piperinic acid by splitting off C_4H_4; and as the product contains only one carboxyl group, the C_4H_4 must have been between the carboxyl of the piperinic acid and the benzene ring. Thus we get for piperinic acid the structure



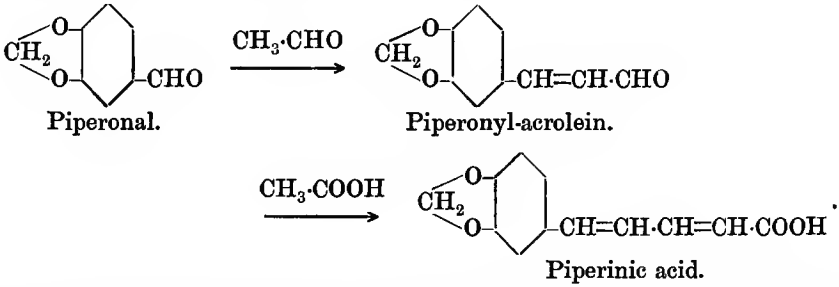
and it only remains to determine the arrangement of the C_4H_4 group. The behaviour of piperinic acid, and especially of its reduction-products, shows that

[1] Rochleder, Wertheim, *Ann.* **54.** 255 (1845); Babo, Keller, *J. pr. Ch.* **72.** 53 (1857).
[2] Rügheimer, *Ber.* **15.** 1390 (1882); Fittig, Remsen, *Ann.* **159.** 142 (1871).

it contains a normal side chain with two double links, and so the only probable formula appears to be this[1]:—



This view is completely supported by Ladenburg and Scholtz's synthesis of piperinic acid.[2] They started with protocatechuic aldehyde, which can be synthesized, and which when treated with methylene iodide gives piperonal.[3] Piperonal condenses with acetaldehyde, when heated with it in very dilute soda solution, to give piperonyl-acrolein. Finally, this product, when heated with acetic anhydride and sodium acetate, condenses after the manner of the Perkin reaction, giving piperinic acid:—



Piperonal. Piperonyl-acrolein. Piperinic acid.

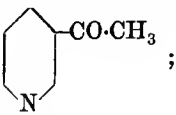
The acid can then be converted into its chloride, and this, as we have seen, combines with piperidine to form piperine, whose complete synthesis is thus possible.

Nicotine

Nicotine occurs in the tobacco leaf, as the salts of citric and malic acids, to the extent of 0·5–8 per cent. Its formula is $C_{10}H_{14}N_2$. It is a di-tertiary base; that is, both its nitrogen atoms are joined to carbon by three bonds. This is shown by the fact that it gives two different quaternary iodomethylates.

On oxidation with nitric acid, chromic acid, or potassium permanganate, it yields nicotinic acid (pyridine β-carboxylic acid). It therefore contains the pyridine nucleus connected to carbon in the β-position.

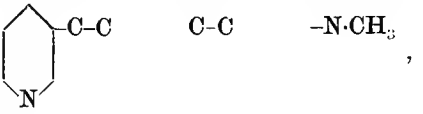
With bromine it gives two different dibromo-compounds—dibromo-cotinine $C_{10}H_{10}Br_2N_2O$, and dibromo-ticonine $C_{10}H_8Br_2N_2O_2$. The first of these gives, on treatment with alkali, methylamine, oxalic acid, and β-methyl-pyridyl ketone,



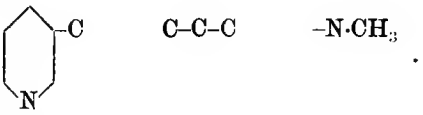
the second gives with alkali methylamine, malonic acid, and nicotinic acid. The formation of methylamine from both of these substances proves that

[1] Fittig, Mielck, *Ann.* **172.** 134 (1874). [2] *Ber.* **27.** 2958 (1894).
[3] Wegscheider, *Mon.* **14.** 382 (1893).

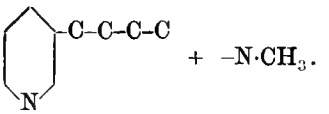
nicotine contains a methyl group attached to nitrogen, and therefore cannot be a dipyridyl compound, as might otherwise be supposed. Further, if we put together the fragments of chains obtained in these two reactions we get from the first:



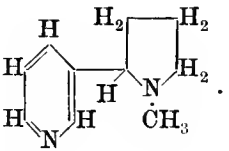
and from the second:—



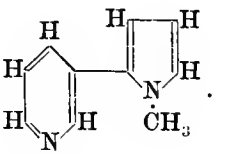
From the fact that we can either split off a 2-carbon chain, and leave two carbons attached to the nucleus, or split off three, and leave one, it follows that these four carbon atoms must form a continuous chain, and the nicotine molecule must contain



Now we have seen that both the nitrogen atoms are tertiary; hence the nitrogen in the pyridine nucleus must be unreduced, and the other nitrogen, which carries the methyl, must be attached to two other carbon atoms as well. This condition is most easily fulfilled if we suppose that this second nitrogen joins up the four carbon atoms of the side chain into a pyrrol nucleus, which would give us for the formula of nicotine:—

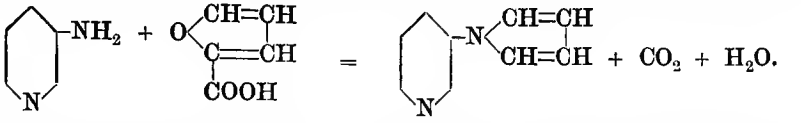


This is confirmed by the fact that if nicotine is gently oxidized by potassium ferricyanide or silver oxide, it is converted into a new base, nicotyrine, with the loss of four hydrogen atoms. This new body must be the corresponding pyridyl-methyl-pyrrol:—

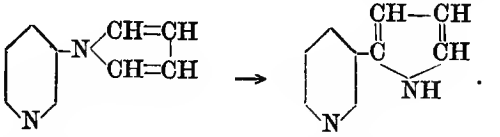


The final confirmation of these views was furnished by the synthesis of nicotine, which was carried out by Amé Pictet.

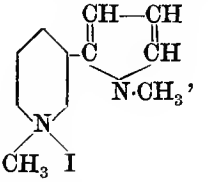
The first stage was the synthesis of nicotyrine. When β-amino-pyridine is heated with pyromucic acid it condenses with it to form N-β-pyridyl-pyrrol :—



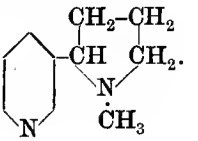
This body when passed through a tube at a low red heat undergoes the same change as the corresponding acetyl- and phenyl-pyrrols, the substituent going from the nitrogen to the β-carbon atom of the pyrrol ring, and β-pyridyl-α-pyrrol is produced :—



On treatment of the product with methyl iodide the imine hydrogen of the pyrrol is replaced by methyl, while the pyridine nitrogen takes up methyl and iodine, becoming pentad. The resulting compound,

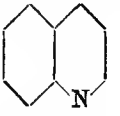


is identical with the iodo-methylate of nicotyrine, and is converted into nicotyrine on treatment with potash. This settles the structure of nicotyrine, and the only stage left was to reduce it to nicotine. For this purpose it was necessary to reduce the pyrrol ring while leaving the pyridine ring unaffected. This was found to be extremely difficult, as both rings behaved alike ; a weak reducing agent reduced neither, and a strong both. It was finally discovered that the end could be attained by first converting the nicotyrine into a mono-iodo-derivative, and then reducing this. In this way a dihydro-nicotyrine was formed, with the two hydrogens on the pyrrol ring ; and this, when treated with bromine and again reduced with tin and hydrochloric acid, gave a base identical with nicotine in composition and in all its properties with the exception of the optical activity. After resolution by means of *d*-tartaric acid, the laevo-base was obtained, which agreed in every respect with the natural nicotine, whose formula was thus proved to be :—

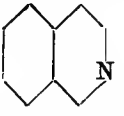


II. QUINOLINE

By the fusion of a pyridine with a benzene nucleus we arrive at benzopyridine, which bears the same relation to pyridine that naphthalene does to benzene, or indol to pyrrol. Owing to the presence of the nitrogen, this may lead to the formation of either of two compounds, according as the two carbon atoms common to both rings occupy on the pyridine ring the α,β- or the β,γ-positions. In the former case we get quinoline, in the latter isoquinoline:—

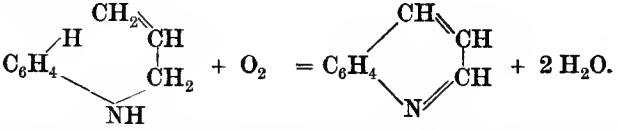


Quinoline.



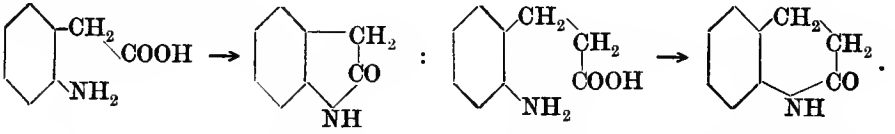
Isoquinoline.

The formula of quinoline was first established by its giving on oxidation a pyridine dicarboxylic acid (quinolinic acid), and by its synthesis from allyl-aniline by passing its vapour over heated lead oxide (the first synthesis of quinoline, Königs, 1879):—



This does not show where the new ring attaches itself to the benzene nucleus, but it shows that the nitrogen is directly attached to the benzene, and so, taken in conjunction with the previous evidence of the existence of a pyridine ring in quinoline, is a sufficient proof of the formula.

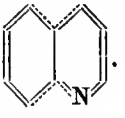
A further proof is given by Baeyer's synthesis from *o*-nitro-hydrocinnamic acid, discovered in 1879, the same year as Königs'. This body on reduction gives *o*-amino-hydrocinnamic acid, which however is unstable, and at once forms its lactame hydrocarbostyril, the ketone of dihydroquinoline. This reaction is exactly parallel to the formation of oxindol from *o*-amino-phenyl-acetic acid; indeed, it was in connexion with his work on the indigo compounds that Baeyer discovered it:—



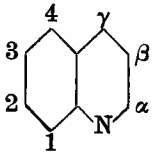
Oxindol. Hydrocarbostyril.

On treatment with phosphorus pentachloride and hydriodic acid hydrocarbostyril loses one oxygen atom and four hydrogens and gives quinoline.

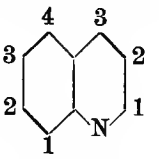
The usual types of formulae have been proposed to express the internal structure of pyridine; the most satisfactory is the analogue of Thiele's naphthalene formula:—



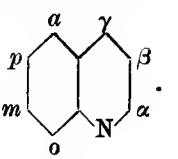
The substitution-products of quinoline are naturally very numerous. As the formula shows, all the seven hydrogen atoms are differently related to the nucleus, and thus seven monosubstitution-products are possible. The numbering of the ring is confusing, as no less than three systems are in use:—



Richter.

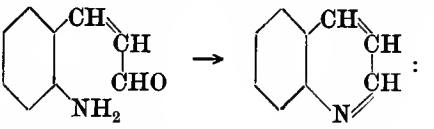


Bz- Py-
Beilstein.

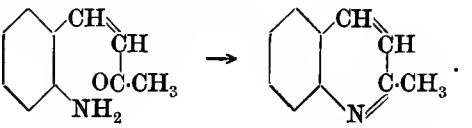


a = ana.

A very large number of syntheses of quinoline and its derivatives are known. They may be obtained by intramolecular condensation from o-amino-derivatives of benzene having a side chain of at least three carbon atoms, and an oxygen atom on the third carbon; e. g. from o-amino-cinnamic aldehyde:—

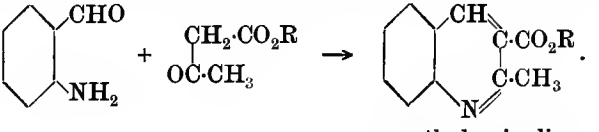


or from o-amino-cinnamyl-methyl ketone:—



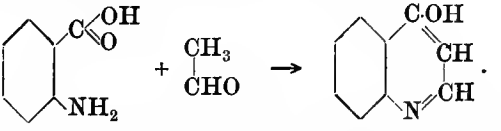
Quinaldine
(α-methyl-quinoline).

A similar reaction is Friedländer's synthesis from o-amino-benzaldehyde and any compound containing a CH_2–CO group, such as aldehydes, ketones, aceto-acetic ester, &c. This occurs in the presence of soda, and depends on the intermediate formation of a benzylidine compound; e. g. with acetoacetic ester:—



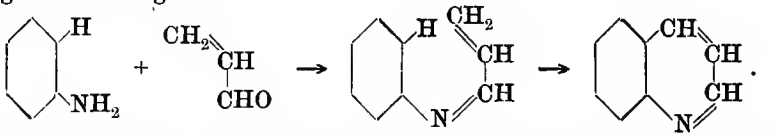
α-methyl-quinoline-
β-carboxylic ester.

By substituting anthranilic acid for o-amino-benzaldehyde we get γ-oxy-quinolines; e. g. with acetaldehyde, γ-oxy-quinoline itself:—

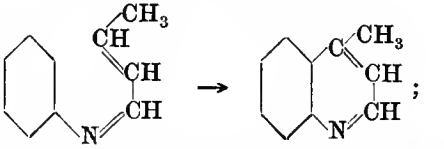


The best known synthesis of quinoline is Skraup's. It consists in heating a primary aromatic amine with concentrated sulphuric acid, glycerine, and an

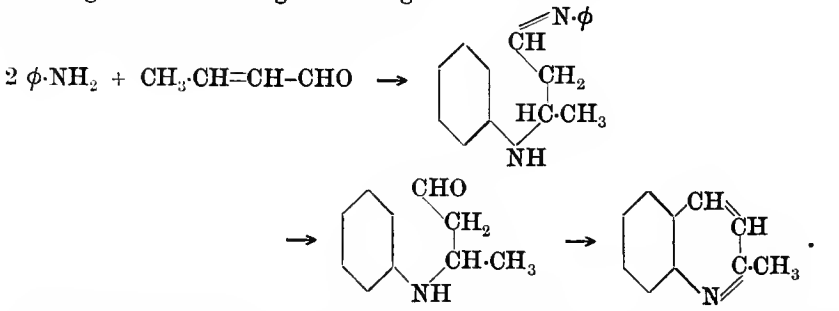
oxidizing agent. The latter is usually the nitro-compound corresponding to the amine employed, which is reduced in the reaction to that amine. Thus, quinoline itself is got from aniline, nitrobenzene, glycerine, and sulphuric acid. We may assume that the glycerine is converted by the sulphuric acid into acrolein, which combines with the aniline to give acrolein-aniline; and then the nitrobenzene oxidizes off the terminal hydrogen of the side chain together with the ortho-hydrogen of the ring:—



There is some reason, however, to think[1] that the reaction in its last stage is not quite so simple as this. If crotonic aldehyde is condensed in this way with aniline, we should expect it to give γ-methyl-quinoline:—

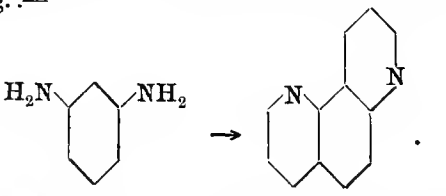


but as a fact the product is α-methyl-quinoline. This can be explained if we suppose that the aldehyde condenses with two molecules of aniline, one of which splits off again in the closing of the ring:—



The Skraup reaction is very violent, and requires great care; the purity of the glycerine seems to be of importance. It has been found[2] that if arsenic acid is used as the oxidizing agent instead of nitrobenzene, the reaction proceeds quite quietly.

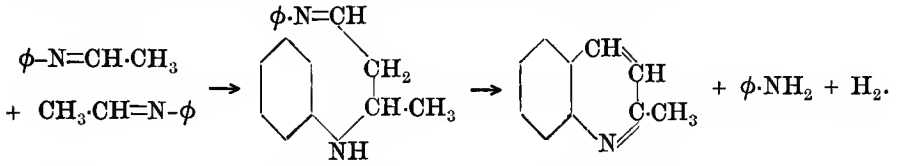
In the place of aniline, any other aromatic amine having at least one ortho position free can be used. Diamines react twice, giving the so-called phenanthrolines; e.g.:—



[1] Blaise, Maire, *C. R.* **144.** 33 (*C.* **07.** i. 974); *Bull. Soc.* [4] **3.** 667 (*C.* **08.** ii. 174); cf. Simon, *C. R.* **144.** 138 (*C.* **07.** i. 973).

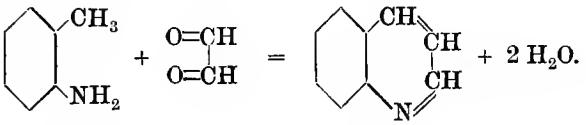
[2] Knüppel, *Ber.* **29.** 704 (1896).

Another general method of great importance for the synthesis of quinoline compounds is that of Döbner and v. Miller, the action of sulphuric or hydrochloric acid on a mixture of an amine and an aldehyde. The reaction proceeds in three stages: (1) the formation of alkylidene-aniline; (2) the formation of a bimolecular condensation-product of this; (3) the loss of aniline and hydrogen to give a quinoline compound, for example with acetaldehyde :—



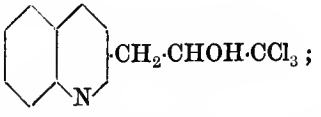
The hydrogen which is set free in this reaction sometimes reduces part of the quinoline compound formed to a tetrahydro-derivative.

Quinoline itself is usually obtained by Skraup's synthesis; it may also be prepared by an extremely simple method due to Kulisch, by warming a mixture of *o*-toluidine and glyoxal with soda:—

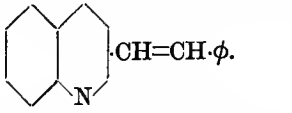


Quinoline is a colourless oil, boiling at 239°. It is very hygroscopic, forming a hydrate ($+1\frac{1}{2}$ H_2O) in moist air. It closely resembles pyridine in behaviour. It is a tertiary base, and forms quaternary quinolinium iodides with the alkyl iodides. The corresponding hydroxides are strong bases; but, as with the pyridinium bases, the oxygen very readily migrates from the nitrogen to the carbon.

Of the homologues of quinoline, the α- and γ-methyl compounds are remarkable for the mobility of the methyl hydrogen. (The same is the case with the picolines.) Thus they condense with aldehydes, either to give compounds of the aldol type, e.g. with chloral,



or with loss of water to form alkylidene derivatives, e.g. with benzaldehyde,

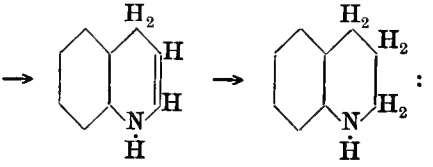


Since the benzene nucleus is more easily substituted than the pyridine, the direct substitution-products of quinoline (for example, with the halogens, sulphuric or nitric acid [1]) contain the substituent in the benzene ring. Those which are substituted in the pyridine ring must be made by indirect methods, as by the

[1] Kaufmann, Hüssy, *Ber.* **41.** 1735 (1908).

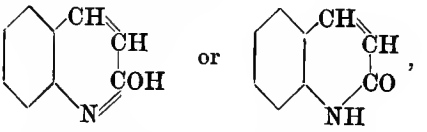
action of phosphorus pentachloride on the oxy-quinolines. These latter resemble the substitution-products of pyridine itself. Thus the α- and γ-chloro-quinolines have the chlorine very mobile and easily replaced.

Quinoline is easily reduced, the hydrogen atoms going almost exclusively to the pyridine ring, as we should expect, since pyridine is more easily reduced than benzene. We thus get first di- and then tetrahydro-quinoline,



which latter behaves as far as the pyridine ring is concerned as a secondary fatty amine, like piperidine: while the benzene ring has the full aromatic character. Precisely the same phenomena occur of course in the case of naphthalene.

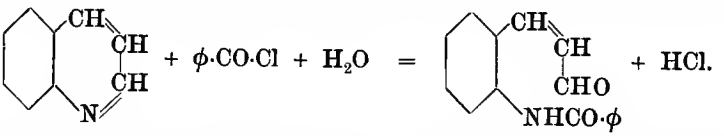
The oxy-quinolines behave at once as acids and as bases. The α- and γ- may be obtained from the chlorine compound with potash. The β- is unknown. They react both as phenols and as ketones. The Bz-oxy-derivatives are prepared by modifications of the syntheses; e. g. from glycerine and aminophenol, with nitrophenol as the oxidizing agent. The most important of the oxy-quinolines is the α-, which is carbostyril,



whose formation by the reduction of *o*-nitro-cinnamic acid has already been mentioned.

It forms salts both with acids and with bases, without opening the ring, but they are very unstable and are decomposed by water. It forms both O- and N-ethers.

The nitrogenous ring of quinoline can be broken by various reagents; thus, benzoyl chloride and soda convert it into *o*-benzoylamino-cinnamic aldehyde [1]:—



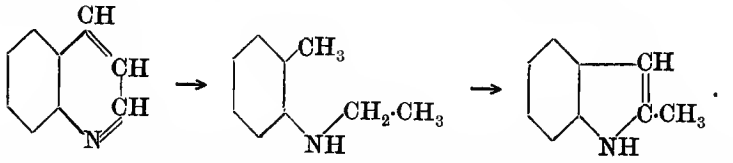
It is to be observed that isoquinoline is not decomposed in this reaction.

In most cases this breaking of the ring is preceded by reduction. Thus if the vapour of quinoline mixed with hydrogen is passed over reduced nickel at 260–280°, α-methyl-indol is formed, together with small quantities of methyl-*o*-toluidine and toluidine.[2] This is the unusual case of the conversion of a 6-ring

[1] Reissert, *Ber.* **38**. 3415 (1905).

[2] Padoa, Carughi, *C.* **06**. ii. 1011.

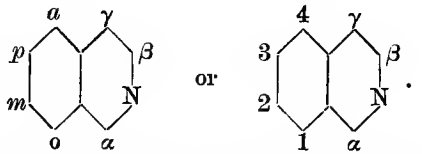
into a 5-ring. It is probably due to the intermediate formation of an open-chain body :—



In the same way tetrahydroquinoline when heated with nickel gives scatol (β-methyl-indol) together with methyl- and ethyl-aniline, which are no doubt intermediate products.[1]

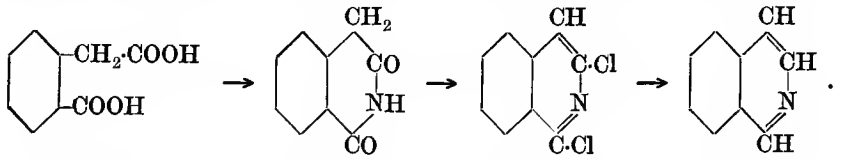
III. ISOQUINOLINE

Isoquinoline is isomeric with quinoline, the two carbon atoms common to both rings being in the β,γ-positions. The positions in the ring are usually numbered thus:—



This group is far less numerous than that of quinoline, but it is interesting from its relation to various natural alkaloids, such as papaverine and berberine.

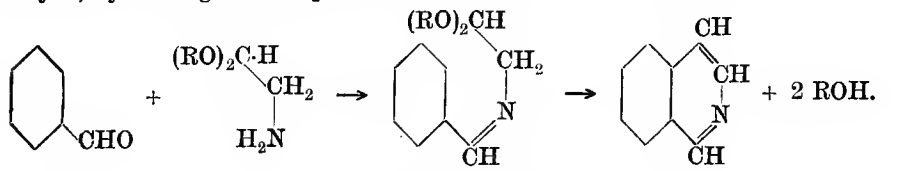
Isoquinoline can be synthesized in various ways. If the ammonium salt of homophthalic acid is heated, it is converted into its imide, which is diketo-tetrahydro-isoquinoline. This, on treatment with phosphorus pentachloride, gives dichloro-isoquinoline, which on reduction yields isoquinoline itself.



Homophthalic acid. | Homophthal-imide. | Dichloro-isoquinoline. | Isoquinoline.

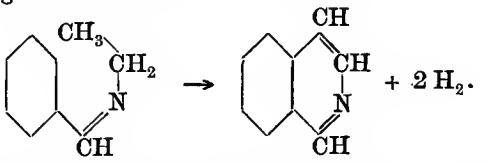
The reaction can also be carried out in one operation, by heating homophthalimide with zinc dust in a stream of hydrogen.

Another general method of obtaining isoquinoline derivatives is to start from benzene derivatives containing the side chain C–N–C–C ; thus from benzylidene-amino-acetal (the condensation-product of benzaldehyde and the acetal of acetaldehyde) by heating with sulphuric acid :—

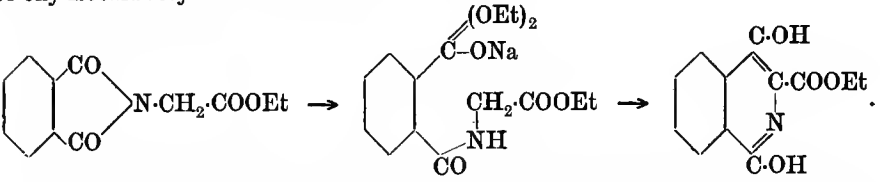


Padoa, Scagliarini, *C.* **08.** ii. 614.

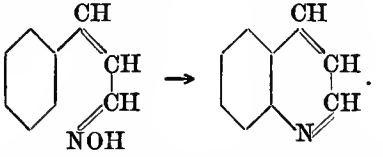
A still simpler synthesis of the same kind is from benzylidene-ethylamine, by passing it through a red-hot tube :—



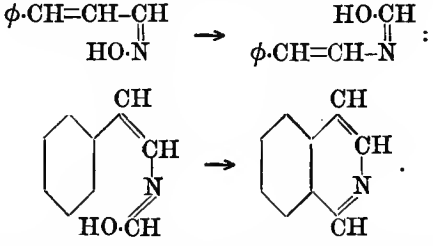
A more unusual method was discovered by Gabriel and Colman,[1] who treated the ester of phthalyl-glycine with sodium ethylate, whereby the carboxylic ester of oxy-isocarbostyril was formed :—



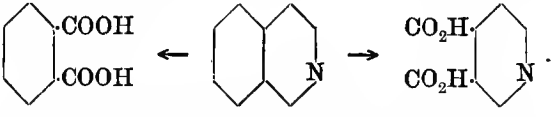
Another remarkable synthesis is by the distillation with phosphorus pentoxide of the oxime of cinnamic aldehyde ; we should expect this to give quinoline :—



As a fact, however, quinoline is not formed, but isoquinoline is, though only in small quantity. This can be explained by supposing that the oxime (as an anti-aldoxime) first undergoes the Beckmann reaction, and then the product condenses :—

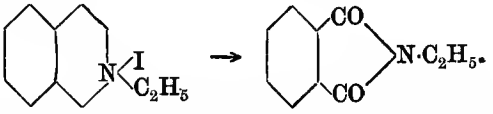


The unreduced isoquinoline compounds are tertiary bases, giving stable salts with acids and quaternary compounds with alkyl iodides. The stability of the pyridine ring is less in isoquinoline than in pyridine itself and in quinoline, as is shown by the fact that when isoquinoline is oxidized in acid solution both the benzene and the pyridine rings are attacked, a mixture of phthalic and cinchomeronic acids being produced :—



[1] *Ber.* **33.** 980 (1900) ; cf. Findeklee, *Ber.* **38.** 3542 (1905).

If the nitrogen is made to assume the pentad condition, the pyridine ring is still further weakened; so that if the halogen alkylates (isoquinolinium salts) are oxidized, the pyridine ring is broken and not the benzene ring. This reaction takes a peculiar course. One carbon is eliminated from the ring, giving an N-substituted phthalimide :—



Isoquinoline occurs among the products of the distillation of coal tar, from which it is separated along with the quinoline. It is isolated by dissolving the raw quinoline in alcohol and adding sulphuric acid, when the less soluble isoquinoline sulphate crystallizes out.

It boils at 240·5° (quinoline at 239°). It is more basic than quinoline, and attracts carbon dioxide from the air.

The derivatives of isoquinoline closely resemble those of quinoline.

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